THE OPSONIC METHOD OF TREATMENT

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A SHORT COMPENDIUM FOR GENERAL PRACTITIONERS, STUDENTS, AND OTHERS

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PREFACE

So prominent a place is this method of treatment now assuming in medical practice, and so scattered is the literature concerning it, that the time seemed ripe for an endeavour to collect such facts as might suffice to give a general idea of the subject. Theories and opinions have been kept within as small bounds as possible, and prominence given to the results achieved in actual practice. No pretence is made of completeness, but it is hoped that the great and ever-increasing utility of opsonic work may have been adequately demonstrated. My best thanks are due to Dr. J. W. Eyre for corrections and suggestions, and for the loan of Charts XI. and XII., and to other friends for revision of certain sections.

Beginners may find it advantageous to defer the reading of Chapter I. until the end.

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CONTENTS

INTRODUCTION

CHAPTER I

OPSONINS: WHAT THEY ARE, THEIR NATURE AND SOURCE

CHAPTER II

DETERMINATION OF THE OPSONIC INDEX

CHAPTER III

PREPARATION OF THE VACCINE

CHAPTER IV

THE OPSONIC INDEX IN HEALTH AND DISEASE: ITS DIAGNOSTIC AND PROGNOSTIC VALUE

CHAPTER V

SCOPE FOR THE EMPLOYMENT OF TUBERCULIN, AND SOME GENERAL RULES FOR THE MANAGEMENT OF TUBERCULAR CASES

CHAPTER VI

STAPHYLOCOCCAL, STREPTOCOCCAL AND PNEUMOCOCCAL INFECTIONS

CHAPTER VII

THE GONOCOCCUS

CHAPTER VIII

THE OPSONIC TREATMENT OF CATARRH, NASAL AND TRACHEAL, AND OF THE ACCESSORY AIR SINUSES

CHAPTER IX

OPSONIC TREATMENT IN CASES DUE TO INFECTION BY THE *BACILLUS COLI COMMUNIS*, *MICROCOCCUS MELITENSIS*, *BACILLUS PARALYTICANS* (OF FORD ROBERTSON), *MICROCOCCUS NEOFORMANS*, AND MENINGOCOCCUS

CHAPTER X

OPSONIC TREATMENT IN EYE DISEASES

THE
OPSONIC METHOD OF TREATMENT

INTRODUCTION

It was in 1798 that Jenner gave to the world the results of his observations and experiments upon small-pox and the production of an artificial immunity against it, under the title 'An Inquiry into the Causes and Effects of the Variola Vaccinæ.'

Although we are as yet ignorant of the cause of small-pox, and can only conjecture upon the nature of vaccination, we have, from analogy with other similar processes, reason for the belief that it consists of an active immunization by the agency of an attenuated form of the causal organism.

In Jennerian vaccination we find the genesis of the opsonic form of treatment, and although the two processes are really very different in nature, the connexion is preserved in the name 'vaccine,' somewhat indiscreetly given to the killed bacterial emulsions now employed. The name is certainly an ill-chosen one, inasmuch as the laity at once think of all the arguments of the conscientious objector, and hesitate about submitting themselves to what they firmly believe to be a process identical with vaccination.

Pasteur carried on the work initiated by Jenner, and endeavoured in divers directions to induce a prophylaxis

by the inoculation, mostly in an attenuated form, of the bacterial agents themselves or products derived from them.

Koch, in 1890, however, was the first to attempt the cure of an infection by a specific remedy—viz., of tuberculosis by means of tuberculin. Unfortunately, doses far in excess of those now employed were used, with the result that tuberculin fell into grave disrepute.

The studies of Leishman on phagocytosis paved the way for the discoveries of Wright upon the bactericidal agents present in the blood, and in especial of the one to which he gave the name of 'opsonin.' Having devised a means of accurately estimating the opsonic content of the blood, he was thereby enabled to learn the reason of the previous failures of tuberculin, more or less to obviate the attendant danger, and place the opsonic method of treatment of tuberculosis upon a scientific basis. The seed he sowed has flourished greatly—how greatly the following pages will briefly indicate—and it would appear that to the genesis of a new, of a scientific, system of medicine the impulse has now been given. The medicine of the future is the medicine of vaccines and of sera. The empiricism of the past will give way to methods based upon scientific knowledge, and the public will no longer look upon medicine with a sceptical eye, and dose themselves with ineffective nostrums. The surgeon will triumph where now he fails, and, armed with additional power, he will not fear the inroads of bacterial invasion.

CHAPTER I

OPSONINS: WHAT THEY ARE, THEIR NATURE AND SOURCE

Of the means whereby the body tissues are enabled to overcome bacterial invasion our knowledge is as yet far from perfect. The process is admittedly a very complex one. Various substances, to which the names 'agglutinins,' 'precipitins,' 'stimulins,' 'lysins,' and 'opsonins,' are given, are considered each to play a part in enabling the phagocytic cells to complete the destruction of the infecting bacteria. Metchnikoff holds that the principal part is played by the substances to which he has given the name 'stimulins.' The presence of these in the tissue fluids he has not yet succeeded in satisfactorily demonstrating, but considers their function to be that of acting upon the phagocytes so as to stimulate them to perform phagocytosis. While not denying the existence of opsonins, he assigns to them but a secondary part. Wright, on the other hand, has demonstrated beyond doubt the presence in the blood of substances which act upon the bacteria, and get them ready for the completion of their destruction by the phagocytes. To these bodies he has given the name of 'opsonins.' It would appear possible for phagocytosis to proceed without prior opsonization of the bacteria, unless it be argued —and this seems very plausible—that the phagocytic cells

contain opsonins in their plasma fluid from which it is hardly possible to free them. Be this as it may, it is beyond question that the presence of opsonin materially assists the processes of phagocytosis.

The method whereby the presence of opsonin in blood-serum is demonstrated is as follows: A little freshly-drawn blood is immediately received into eight or ten times its volume of 2 per cent. sodium citrate to prevent coagulation. The blood-cells are then thrown down by rapidly centrifuging, and the supernatant liquid pipetted off. The cells are then thoroughly washed with a considerable bulk of a solution of 0·8 per cent. sodium chloride in distilled water, and again thrown down by means of the centrifuge, this process being repeated two or three times, so that finally the cells are washed practically free from all blood-plasma, and are left suspended in a very small volume of the normal saline solution, as uniform a mixture as possible being made. A twelve to eighteen hour old culture on agar of any organism—say *Staphylococcus albus*—is then taken, and a thick emulsion made with a solution of 0·1 per cent. sodium chloride in distilled water. Clumps are thrown down by means of the centrifuge, and the bacterial emulsion divided into two parts, *A* and *B*. *A* is set aside ; to *B* an equal volume of fresh blood-serum is added, and the two thoroughly mixed together and heated in an incubator at 37° C. for fifteen minutes. The bacteria are then thrown down by means of the centrifuge, and as much liquid as possible pipetted off. The bacteria are well washed with 0·1 per cent. solution of sodium chloride in distilled water, and again thrown down, this process being repeated several times. Finally, an emulsion of the bacteria is made in the salt solution exactly like *A*, and the numbers present respectively in emulsions

A and *B* counted, the thicker emulsion being then diluted to exactly the same strength as the weaker. We have then a suspension of blood-cells of which unit volumes contain the same number of polymorphonuclear white cells—*i.e.*, of phagocytes—and two emulsions of the same strength of a given organism in 0·1 per cent. salt solution, differing only in the fact that the bacteria in one (*B*) have been acted upon by blood-serum at 37° C. for fifteen minutes. If this has had no action upon the organisms, then identical results should be obtained by the following procedure : Equal volumes of the blood-cells and the bacterial emulsion *A* are then thoroughly mixed together in a capillary pipette and incubated at 37° C. for fifteen minutes, the same being done with the substitution of emulsion *B* for *A*. Films are then spread, stained by Leishman's method, and observed under a $\frac{1}{12}$-inch oil-immersion lens. The number of bacteria engorged by 100 polymorphonuclear leucocytes is then counted upon each film. An experiment performed in this way gave the following result :

Bacterial Emulsion employed.	Number of Cocci in 100 Polymorphonuclear Leucocytes.
A	10
B	500

It is thus obvious that some change is produced in the bacteria by the action of the blood-serum whereby phagocytosis is expedited. To the substance by which this change is brought about Wright gave the name ' opsonin.'

The Nature of Opsonins.

Whether the opsonic power of sera is due to the presence therein of substances unrecognized before the discoveries

of Wright and Douglas, or whether it is a special function of the usual immune bodies of sera, is still a matter of dispute. Wright and Douglas, Bullock and Atkin, Keith, Hektoen, Barratt, Neufeld, and others, hold the former view. Savtchenko and Dean consider that opsonins are identical with the amboceptors of serum. Muir and Martin have advanced evidence that opsonization depends upon the co-operation of two substances, one of which closely resembles complement of serum in certain of its biological properties ; while Levaditi and Inmann assert that opsonins are nothing but complements. In some respects opsonins bear slight resemblance to ferments. Thus, Wright and Douglas found that normal serum can be diluted twenty-four fold with only a comparatively slight lessening of its opsonic power when compared with undiluted normal serum. A possible fallacy however in this observation will be mentioned later.

Secondly, opsonins are thermolabile—that is, destroyed by heating the serum for fifteen minutes to a temperature of 60° C.

Noguchi[1] has, however, shown that they are not destroyed by drying the serum at 23° C., and that in this desiccated serum they retain their activity after two years. In this dried state, like ferments, they are much more resistant to heat. Exposure to a temperature of 120° C. but slightly impairs their power, which is not altogether destroyed by a temperature of 150° C.

In these respects, as well as in their sensitiveness to slight increases in the acidity or alkalinity of the medium in which they are dissolved, opsonins acting best in a neutral medium, they bear a distinct resemblance to ferments, but here this similarity seems to end.

[1] *Journal of Experimental Medicine*, vol. ix., No. 4, p. 455.

Opsonins of a Proteid Nature.

Yorke[1] filtered normal serum through a sterile Chamberland candle under very high pressure, and found that the opsonin passed readily through for the first few minutes, but that after that only traces permeated the candle wall, owing to the pores being filled up by the proteids of the serum. The residue in the filter, beside containing comparatively unaltered serum, consisted also of a gelatinous substance adherent to the sides of the candle and of high opsonic power. It would thus appear that opsonins will not pass through a Chamberland candle the pores of which have been blocked up with gelatine or proteid substance. They are, therefore, of a 'colloidal' nature. Inasmuch as they have also been shown by Tamar and Bispham,[2] and confirmed by Yorke (*vide supra*), not to be dialysable, and are also carried down by euglobulin when serum is half saturated with ammonium sulphate, the view that they are of the nature of a proteid is rendered highly probable.

Their exact character obviously cannot, however, be determined until they have been isolated and obtained in a state of purity.

The Relationship to Infection of the Opsonic Index.

Whether fall of index be antecedent to or the result of infection it is impossible as yet to determine, but the following observation clearly shows that infection and lowered index go hand in hand: A case of chronic cold

[1] *Bio-chemical Journal*, vol. ii., June, 1907, p. 357.
Journal of Experimental Medicine, December, 1906.

due to Friedlander's bacillus that had been injected some time previously with the corresponding vaccine had an index of 2·6. Twelve hours later an acute attack began to come on with sneezing and shivery feeling. A specimen of blood was taken, and the index found to have fallen to 2·0. Prompt treatment was adopted and an injection of vaccine given, which stopped further progress of the oncoming cold.

That the fall of index is antecedent to, and not the result of, infection is rendered highly probable by the recent demonstration, referred to later, of the existence of specific and non-specific antiopsonins, often of a simple chemical constitution, and by the following consideration : Many people, otherwise perfectly free from acne, frequently develop a crop of pustules when suffering from constipation. Their resistance—*i.e.*, their opsonic index to staphylococcus—is usually normal, but may be assumed to be so lowered by the absorption of toxins—*i.e.*, of antiopsonins—from the bowel that infection then occurs. Infection having occurred, their index may remain low, in which event the acne will become chronic, or rise to or over normal, in which case recovery soon ensues.

Per contra, the throwing off of an infection is accompanied by rise of index. An old sufferer from chronic colds who had been injected a month previously had an index to Friedlander's bacillus of 1·5. All the symptoms of a fresh cold appeared, but, as the patient said, he felt he had the cold beaten from the start, and little wonder, for in twenty-four hours the index rose to 5·8, and the patient was perfectly well.

Site of Formation of Opsonins.

That preopsonin or opsonin is not formed in the blood is practically certain. The amount of opsonin present in the blood bears no definite relation soever to leucocytosis, nor is it affected by disease of the blood-forming organs. Evidence is forthcoming that it is a product of muscular or subcutaneous activity. Allen has shown both in man and animals that if limbs be thoroughly perfused with normal salt solution to remove all blood, and the muscles cooled and minced, and their plasma extracted in the usual manner, that the index of this plasma, despite slight dilution with the saline solution used in the perfusion, is markedly higher than that of the blood-serum towards various organisms. In the instance of an amputated leg the index of the muscle-plasma compared with that of the patient's serum was 1·4 towards the bacillus of Friedlander, the tubercle bacillus, and *Staphylococcus aureus*. In another case it was found to be 1·3.

The only possible conclusion is that actual formation of opsonin occurs in the muscle tissues, and passes thence into the blood. This is confirmed by the experience of Wright[1] that a certain case of tubercular ulceration which had previously defied treatment did well when the tuberculin was injected in a concentric manner around the area of ulceration.

Fate of Opsonins in the Organism.

As regards this question but little is known. It, however, appears that all exudates and secretions contain

[1] *Lancet*, August 24, 1907, p. 494.

certain amounts of opsonin. Lawson[1] finds that it is contained in appreciable amount in the sweat, and to a larger degree in the urine, and that this excreted opsonin is increased during a negative phase consequent upon the injection of a bacterial vaccine. Milk also contains opsonin, perhaps to the extent of a quarter or a fifth of that of the blood. Inasmuch as opsonins are practically absent from the blood of the newly-born infant, and gradually attain a maximum during the first few weeks, the question as to whether the opsonin of the mother's milk can be absorbed through the alimentary tract of the infant attains considerable importance, but has not yet been decided.

The Question of the Specificity and Multiplicity of Opsonins.

The earlier experiments of Bullock and Western tended to show that the blood-serum contained a large number of opsonins, each specific for a given organism. This they demonstrated in two ways. In the first they tested the opsonic power of a given serum against both *Staphylococcus albus* and tubercle bacillus. The serum was then mixed with one or other of these microbes, and after fifteen minutes' incubation at 37° C. the mixture was centrifuged until the bacteria were all thrown down. The opsonic power of the supernatant liquid was then again tested for both organisms. They found it had been deprived of its opsonin for the microbe with which it had been digested, while it largely retained its opsonin for the microbe with which it had not been digested.

In the second class of experiment the serum of human

[1] *Lancet*, September 7, 1907, p. 704.

beings was tested repeatedly against both staphylococcus and the tubercle bacillus. Injections of tuberculin were then given, and found to produce a rise in the tuberculo-opsonin, while not affecting the staphylococcic opsonin, and *vice versa*. The fact, too, that infected patients are found to have either a high or a low index towards that particular organism, and a normal index towards all others, was held to point in the same direction. This view leads, however, to the rather absurd conclusion that there are as many opsonins produced by the human body as there are varieties of bacteria.

Yorke and Smith[1] demonstrated the fallacy of Bullock and Western's experiments, and pointed out that they failed to incubate the serum with a sufficiently large number of the organisms. By incubating normal serum with very large numbers of a given bacillus for varying times (fifteen, thirty, sixty minutes), and proceeding exactly like Bullock and Western, they found that it was impossible to separate from normal serum any one opsonin by adding the particular organism to it and incubating, and to leave intact at the same time the opsonins corresponding to other organisms. This is well shown by the following experiment of theirs: A strong emulsion of anthrax bacilli was made in 0·9 per cent. NaCl solution, and killed by heating at 100° C. for thirty minutes. The bacilli were then thrown down by centrifuge, and washed thrice with 0·9 per cent. NaCl solution. The washed dead bacteria were then made up into a strong emulsion, and added to two equal portions of normal serum (*A* and *B*).

A was incubated at 37° C. for thirty minutes, *B* for sixty minutes.

[1] *Bio-chemical Journal*, vol. ii., December 19, 1906.

The bacteria were then thrown down, and the supernatant sera tested for opsonin with staphylococcus and anthrax. The control sera were diluted to an equal extent with 0·9 per cent. NaCl solution and incubated for similar times with the like organismal emulsions. The figures obtained from the films prepared were as follows :

TABLE I

	Number of Bacteria phagocytosed by 50 Leucocytes.	Index.
A.—I. Anthrax :		
Control serum	40	1·00
Treated serum	8	0·20
II. Staphylococcus :		
Control serum	341	1·00
Treated serum	87	0·25
B.—I. Anthrax :		
Control serum	48	1·00
Treated serum	2	0·04
II. Staphylococcus :		
Control serum	395	1·00
Treated serum	70	0·17

Other experiments gave similar results. It therefore appears that the incubation of a large number of any organism with serum will not only greatly reduce the contained opsonin for that given organism, but those for other organisms as well. The fall in index is apparently general, and the phenomenon is most easily explicable upon the supposition that there is in normal serum a single body or ' preopsonin ' from which, under appropriate stimulation by certain bacteria, there can be split off the particular opsonins for the given bacteria.

The greater the number of any kind of bacteria added to any portion of serum, the more specific opsonin it is necessary for the preopsonin to form. The latter is thus reduced in quantity, and hence less of other specific

opsonins are formed when other organisms are added to the serum. This will account for the general lowering of the opsonic indices noted.

The specific rise of the opsonic index noted after the injection of a vaccine may be explained by assuming that certain of the opsonin-forming cells are stimulated to form a specific opsonin, instead of, or in addition to, the general pre-opsonin which they are normally pouring out into the serum.

Further confirmation of these views is afforded by the results of injection of various antitoxic and antibacterial sera. If a healthy man be injected with antitetanic serum, a specific rise in the tetano-opsonic index first occurs. This is followed, however, by a general fall. Thus, the staphylococcal, tuberculo-, and tetano-opsonic indices all fall below normal (Yorke and Smith[1]). A similar though less marked general depression is observed after injection of antistreptococcal or antidiphtheritic serum. R. Bradshaw[2] has recorded the following observations upon the effect of injections of anti-diphtheritic serum upon the tuberculo-opsonic index.

TABLE II

No. of Case.	Interval since Anti-diphtheritic Serum given.	Index.
1	2 days	1·30
1	5 ,,	0·64
2	12 ,,	1·02
2	25 ,,	0·35
3	27 ,,	0·89
3	41 ,,	0·72
4	25 ,,	0·64
5	26 ,,	0·72
6	26 ,,	0·62
7	27 ,,	0·77
8	28 ,,	0·69
9	3 months	0·47

[1] *Bio-chemical Journal*, 1906, p. 341.
[2] *Lancet*, May 19, 1906, p. 1387.

Other observers do not, however, altogether agree with these observations of Bradshaw, but find that the initial fall does not usually last nearly so long as is indicated above, and is followed by a pronounced subsequent rise. So much is this the case that marked improvement is claimed to have been observed in tubercular subjects to whom antidiphtheritic serum has been administered.

The experiments of Hektoen and Ruediger[1] confirm the conclusion that the injection of these sera results in the formation of specific antiopsonins. They found that many substances, such as calcium and barium chlorides, sodium bicarbonate, lactic acid, and alcohol, are non-specific antiopsonins.

That these specific and non-specific antiopsonins cause a general fall in the opsonic action of the blood seems, then, to favour the view that in normal serum there are probably not a considerable number of distinct opsonins, but rather one preopsonin from which the former can be split off. As regards the blood-serum of infected individuals, it would appear that actual specificity of opsonin does probably exist. An important observation bearing upon this point is that the opsonin of the blood-serum of an infected person—*i.e.*, of an 'immune serum' —appears to possess greater thermostability than that of a normal person. Upon Wright's assumption that the opsonins of normal and immune sera are identical this appears very difficult of explanation, and it seems possible that the immune serum contains a thermostabile constituent absent in the normal serum. At present this point must be held not to have been definitely settled.

[1] *Journal of American Medical Association*, May, 1906.

Effect upon the Opsonic Index of Injection of a Bacterial Vaccine.

The statement is usually made that the result of the injection of a bacterial vaccine upon the index to that organism of a healthy person is very slight. Any subsequent depression of the index is stated to be of a very temporary character and of only small extent, while the rise of index which follows the return to the normal is also of a limited and slight character. This statement is substantially true for the tubercle bacillus, but does not hold equally for other organisms, as the following experiments will show :

Experiment I.—An injection of 250,000,000 dead organisms of the *Bacillus septus* was given to a healthy person not infected by that organism, and samples of blood taken on injection and after intervals of three, six, twelve, eighteen, twenty-four, thirty-six, forty-eight, seventy-two, and ninety-six hours. The comparative opsonizing powers of the various sera towards the *Bacillus septus* were then determined in the usual manner, with the following results :

TABLE III

Serum 1	on injection			882	bacilli	in	200	cells.	Index = 1·00
,, 2	after 3	hours		544	,,	,,	,,		0·62
,, 3	,, 6	,,		885	,,	,,	,,		1·00
,, 4	,, 12	,,		804	,,	,,	,,		0·91
,, 5	,, 18	,,		949	,,	,,	,,		1·08
,, 6	,, 24	,,	1,096		,,	,,	,,		1·25
,, 7	,, 36	,,	1,000		,,	,,	,,		1·15
,, 8	,, 48	,,	1,044		,,	,,	,,		1·20
,, 9	,, 72	,,	1,220		,,	,,	,,		1·38
,, 10	,, 96	,,	1,248		,,	,,	,,		1·39

Experiment II.—An exactly similar experiment was done upon a second healthy individual, 350,000,000

organisms of the *Micrococcus catarrhalis* being injected, with the following result :

TABLE IV

Serum 1 before injection				942	cocci in 200	cells.	Index = 1·00
,, 2 after	3	hours		722	,, ,,	,,	0·77
,, 3 ,,	6	,,		580	,, ,,	,,	0·62
,, 4 ,,	9	,,		825	,, ,,	,,	0·88
,, 5 ,,	15	,,		1,125	,, ,,	,,	1·20
,, 6 ,,	22	,,		1,080	,, ,,	,,	1·15
,, 7 ,,	28	,,		1,131	,, ,,	,,	1·20

In both of these experiments we see a very pronounced depression indeed produced in the index, in each case to the extent of 0·4. The duration of this depression was short, it is true, but no shorter than that obtained in a similar experiment upon an infected person, as is seen in

Experiment III.—From the tracheal mucus and nasal secretion of an individual who had been suffering for a fortnight with a very bad tracheal cough a practically pure culture of the *Micrococcus catarrhalis* was isolated, and the index found to be 0·56. An injection of 250,000,000 organisms was given, and the effect upon the index determined as follows, the index prior to injection being called unity :

TABLE V

Serum 1 before injection				140	cocci in 100	cells.	Index = 1·00
,, 2	4	hours	after	90	,, ,,	,,	0·64
,, 3	8	,,	,,	220	,, ,,	,,	1·57
,, 4	12	,,	,,	280	,, ,,	,,	2·00
,, 5	15	,,	,,	312	,, ,,	,,	2·23
,, 6	18	,,	,,	325	,, ,,	,,	2·32

The chief difference is the much more pronounced subsequent elevation of index. To the depression of the index the term ' negative phase ' was given by Wright, while the subsequent rise he called the ' positive phase.'

The negative phase thus comprises the interval when the index is falling, and also that when it is rising until the level at which it stood prior to injection is again attained. The full rise having been attained, the crest of the positive phase may be said to have been reached, as at seventy-two hours in Experiment I. and at fifteen hours in Experiment II. (*supra*). The index remains practically steady at this elevated level for a time, which varies in different individuals and for different organisms—it may be for hours, days, or even weeks. This may be termed the 'positive phase plateau.' It then begins to fall, and falls with a rapidity which also differs in different cases.

During the period of falling in the negative phase the patient may present marked clinical features. For instance, in cases of acne a fresh crop of pustules usually appears; in cases of cold the cold gets worse; in tubercular cases the patient may feel restless and ill or experience increased pain in a joint. Only rarely is the temperature, pulse, or respiration markedly affected. Very soon indeed after the inception of the rise, even before the index has reached the level at which it stood prior to injection, the patient may begin to improve and declare himself to feel better.

A very marked instance of this was afforded in the case of a severe gonococcal conjunctivitis, in which the pain, discharge, and chemosis all diminished two days before the index had reached the level at which it originally stood. *The* factor in improvement would, therefore, appear to be a 'rising' index.

It must, however, be mentioned that the above is not a complete description of all that occurs or may occur after the injection of a bacterial vaccine, and other variations may be introduced by modifications in the dosage.

Thus, it is probable that with a medium dose the first effect is a very slight and very transient fall indeed of the index, due to the immediate combination of the opsonin at the site of injection with antiopsonin present in the vaccine. To this the body makes reaction by formation of fresh opsonin, with the result that there ensues a short period of slightly raised index, and it would appear that the improvement sometimes seen during the supposed ' negative ' phase is in reality due to this initial temporary rise.

After this oscillation the true negative phase begins, to be succeeded by the positive phase, though fresh oscillations may occur at any period.

With minimum doses of a vaccine, on the other hand, all oscillations and the negative phase itself may be elided, and injection be followed by an immediate rise, limited alike in extent and duration.

Duration of Negative Phase in Phthisis.

Lawson and Stewart[1] investigated the duration of the negative phase in 120 cases of phthisis. Their results were as follows :

No negative phase in 15 cases.
Persistent negative phase in 21 cases.
Negative phase lasting—

1,	2,	3,	4,	5,	6,	7,	8,	9,	10,	11,	12,	13,	14 days.
in 14,	12,	10,	5,	7,	4,	10,	4,	4,	3,	4,	1,	1,	5 cases.

Total 84 cases.

The pulse and respiration did not appear to be affected at all, while the temperature showed no response during the negative phase in 50 per cent. of cases. It would thus appear that in 41 per cent. of the cases the negative

[1] *Lancet*, December 9, 1905, p. 1682.

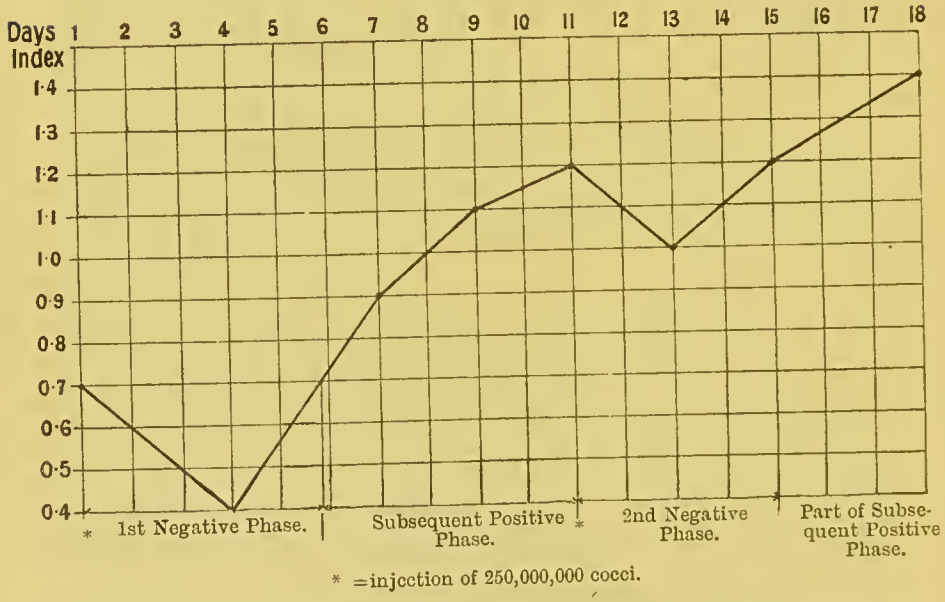
phase lasted over a week. Upon the yet more important questions as to the interval occupied in various cases in attaining the crest of the positive phase and the duration of the plateau published information is lacking.

The significance of a persistent negative phase after a first injection of tuberculin is great. It may mean that the case is one altogether unsuited to this course of treatment on account of the immunizing machinery having altogether broken down ; it may mean that the initial dose was much too large, in which case it is unnecessary to wait any longer than until all constitutional symptoms have disappeared before reinoculating at this level with a much diminished dose, or it may be merely a peculiar phenomenon that the author has several times experienced especially in chronic gonorrhœal cases. As subsequent events showed, the immunizing machinery was far from exhausted, nor was the dose too large, yet the index fell markedly, and there it remained for weeks at a new low level. The repetition of the original dose resulted in a perfectly satisfactory response, as did all subsequent injections. In these instances, then, it is probably good practice, except in obviously bad cases, to repeat the original dose a second time. A further fall and persistence of the negative phase would be warning to wait a few weeks and then begin again with a dose only a third or quarter as great as that previously employed. Yet, again, in cases which have been doing well and had several injections the usual dose will produce an unexpectedly long negative phase, lasting for three, four, or five weeks, although the patient apparently continues to improve. What this means I know not at all, but the safer course appears to be to wait overlong rather than to get impatient and inject prematurely.

The Cumulation of Negative and of Positive Phases.

A second injection during a negative phase will result in further depression of the index to yet a lower level—that is, one negative phase may be superimposed upon another. The same holds true for positive phases, and this production of cumulated positive phases is the great aim in opsonic treatment, for in this way the index may be raised to a very high level. It still remains true, however, that the first result of an injection is to produce a negative phase, so that a slight lowering of the raised index at first results, to be followed by a further rise. This cumulation of positive phases may be thus shown diagrammatically (Chart I.):

CHART I



* =injection of 250,000,000 cocci.

It is generally held that this much-to-be-desired object is unattainable in the case of tuberculin injections; that a cumulation of positive phases cannot be produced, and

that each injection is to be conducted as if a new case were being begun, except that gradually increasing doses are to be employed. While this is generally true, frequent determination of the index will sometimes enable the psychological moment to be seized, and a cumulation of positive phases to be produced. A few additional cases seem, again, to be especially predisposed to such a result.

In tubercular cases, then, it is customary to allow the good effects of one injection, produced by the resultant positive phase, to take full effect before again inoculating. This means, as a rule, an interval of about three weeks between successive inoculations. In other infections the aim always is to superimpose one positive phase upon another. To this end a fresh injection is given while the previous positive phase is still on, and the best time is coincident with the attainment of the crest or a day or two after, rather than when the index has again begun to descend.

Regulation of Dosage.

That doses of appropriate magnitude be employed is of importance secondary not even to proper spacing of the several inoculations. Experience has shown that the proper initial dose varies considerably for different organisms and to a less extent for different persons. The average initial dose for each organism is given later. Let us suppose that this dose has been given in a certain instance, the index prior to inoculation having been found to be subnormal. A fresh determination of the index is made twenty-four hours after injection, and again seven or ten days later.

The various possible results and the deductions therefrom may be thus displayed schematically :

Index 24 Hours after Injection.	Index 7 or 10 Days Later.	Deduction.
Slight fall	Further fall	Dose too large
Slight rise	But little altered	Dose too small
Slight fall	Marked rise	Dose correct

It will be found, as treatment progresses, that gradually increasing doses, often at shorter intervals, have to be employed to produce any marked effect upon the index. Thus, in staphylococcal cases the initial dose of 250,000,000 organisms may have finally to be increased even to 5,000,000,000 before a cure is effected. So long as a certain dose produces an adequate response increase of it is not advisable, but so soon as this result is not achieved the indication for doubling the dose is present. The approaching termination of infection is indicated when these large doses finally fail to produce a rise of more than one or two decimal points in the index, which assumes a level at unity or slightly above it. One or two more large doses are then to be followed by diminished doses at increasing intervals.

Other Methods of Raising the Opsonic Index.

Injections of bacterial vaccine are not the sole means whereby the opsonic index may be raised. Applications of heat and massage probably have their good effect by acting locally in this manner.

It has been shown that Bier's treatment by passive congestion has the effect of raising the general opsonic power of the blood to an infecting organism, while nuclein injected subcutaneously and yeast by the mouth (Huggard

and Moreland[1]) have a similar action. This explains the well-known therapeutic action of yeast in erysipelas, furunculosis, and acne, and the varied results obtained by its administration uncontrolled by the opsonic index.

Malden[2] showed that its action was probably due to the nucleo-albumins it contained.

It has been already mentioned that the administration of antidiphtheritic serum produces a temporary fall in the tuberculo-opsonic index, which is followed by a subsequent rise.

Bosanquet and French[3] studied the effect of Marmorek's antituberculous serum upon the tuberculo-opsonic index in five cases. They found that, when given subcutaneously in one case, an alarming fall in the index from 1·05 to 0·25 occurred ; cessation of the injections was followed by a rapid rise to 1·45.

In the other four cases the rectal method of administration was followed. In three of these a rise in the index was produced, usually after three or four daily doses had been given. A maximum index was soon reached, and continued with slight oscillations for three or four weeks while the serum was being given, and for about a week subsequently. In the fourth case, which was a very advanced one, the index fell from 1·75 to 0·8 during treatment, recovering subsequently slowly to 1·0.

It would thus appear probable that in certain instances the beneficial results of antisera may be, at all events, partly due to the elevation produced in the opsonic index.

[1] *Lancet*, June 3, 1905.
[2] *British Medical Journal*, July 1, 1905.
[3] *Ibid.*, April 13, 1907, p. 862.

Elevation of the Opsonic Index not the Sole Necessity.

Wright has been at especial pains to point out that the successful combat of bacterial invasion does not depend upon elevation of the opsonic index alone. Increase in the bacteriotropic substances of the blood having been secured, it still remains to ensure that these be brought in sufficient amount to the point of attack. Experiment has shown that the fluid portion of pus may be entirely free from opsonin, while the amount of the latter in the serous exudates in pathological conditions of the peritoneum, meninges, pleura, and pericardium may be very greatly diminished. It therefore becomes necessary to ensure the removal of the fluid poor in antibacterial substances, and its partial replacement by lymph rich in such substances. This end is secured in various ways, as by opening a fluctuating abscess, doing a laparotomy upon a tubercular peritonitis, or tapping an empyema. Other cases there are, such as more or less non-discharging sinuses, where dense granulation tissue and deposits of fibrin prevent free access of lymph, and brawny swellings where the same result is brought about by blockage of the lymphatics. The former of these conditions Wright meets by the introduction into the sinus of a solution of 0·5 per cent. citrate of soda and 5 per cent. sodium chloride, the former decalcifying the lymph, and so preventing its coagulation, the latter by osmosis causing transudation of fluid from the vessels.

The surgeon has been wont to secure a similar result by scraping and the application of caustics. Brawny swellings are to be freely incised, and the coagulability of the lymph diminished by three hourly doses of 60 grains of sodium citrate. Further consideration is given to this question in later pages.

CHAPTER II

DETERMINATION OF THE OPSONIC INDEX

Definition of the Opsonic Index.

The opsonic index may be defined as the ratio:

$$\frac{\text{Opsonic content of unit volume of the patient's blood-serum}}{\text{A normal person's}}.$$

This is now determined according to a method first introduced by Leishman for the estimation of the phagocytic power of blood. Other methods have been employed, but need not be referred to, as they have been completely superseded by Wright's modification of the above.

The following materials and apparatus are required:

1. A sufficient quantity of the patient's blood-serum and of that of the normal person.

2. Blood-cells which have been thoroughly freed from the plasma in which they normally float.

3. An emulsion of the bacterium towards which the opsonic index of the patient is to be determined.

4. Glass-tubing $\frac{3}{16}$ inch and $\frac{5}{16}$ inch in external diameter —the smaller for collection of the blood samples, the larger for the opsonic determinations. The former are to be cut into lengths of about 3 inches, and drawn out into capillary threads at each end, which are then cut off short. The latter are to be drawn out at one end only into fine capillary threads about 6 inches long and as far as possible of uniform bore.

5. Strong rubber teats, file, grease pencil.

6. Centrifuge with hæmatocrite attachment, and glass tubes to fit the same.

7. Watch-glasses and platinum loop.

8. The following solutions in sterile distilled water, carefully freed from dust and hairs, not by filtering, but by centrifugalization :

(*a*) 1·5 per cent. to 2 per cent. neutral sodium citrate.

(*b*) 0·8 per cent. sodium chloride.

(*c*) 0·1 per cent. sodium chloride.

9. Glass slides thoroughly grease free.

10. Incubator (Hearson's biological), maintained at 37° C.

11. Methylic alcohol for fixing.

12. Appropriate staining solutions—viz., for all organisms except tubercle, Leishman's stain ; for tubercle, carbol fuchsin, 20 per cent. sulphuric acid, absolute alcohol, and toluedene blue.

13. Porcelain jar with metal cover for holding slides during fixing and staining.

14. Microscope with $\frac{1}{12}$-inch oil-immersion lens and mechanical stage ; cedar-wood oil.

The following procedure is then to be adopted :

1. *Collection of Blood for Serum.*—This is done by cleansing the finger-tip or lobe of the ear with warm soap-and-water or 2 per cent. lysol solution, drying, and rubbing well with a small piece of lint saturated with ether. When the latter has evaporated, a prick is made with a needle. This is best done decisively, for patients prefer one effective puncture to several ineffective ones. As a rule, they prefer the finger-tip to be utilized, but

should the epidermis be obviously thick at the root of the nail, it is better to employ the lobe of the ear. The blood must flow spontaneously, or but very slight pressure be employed, and the first drop wiped away, for, as has been shown, the opsonic content of the plasma of muscle and the subcutaneous tissues is considerably higher than that of the blood. On approximating one of the capillary ends of the tube to the blood, the latter will flow spontaneously into it. Three or four drops of blood will suffice. The tube must now be sealed off, and here a word of caution is necessary. Opsonins are readily destroyed by heating to 60° C. ; the blood must, therefore, not be heated. All risk of this is avoided by gently warming the end of the tube away from the blood, and then sealing off this end. Lay the tube down flat, and allow it to cool. In doing so the blood is sucked back from the unsealed capillary end by the vacuum produced by the contraction of the contained air as it cools. When this has occurred, that end also may be sealed off in the tip of the flame. These precautions are far from unnecessary, for I have seen many samples of blood quite spoilt in the collecting.

2. *Preparation of the Blood-Cells.*—It matters not whence the blood for this purpose is collected provided not from a sufferer from disease of the lymphatic system. The blood may be collected from the patient at the same time as the sample for the blood-serum. It should, however, be done aseptically to prevent contamination with organisms which will grow rapidly in such a favourable medium, and prove troublesome, perhaps, when the time comes for counting the slides. The collection is done in one of the $\frac{5}{10}$-inch glass pipettes, to which a strong rubber teat has been fixed. A little of the sodium citrate solution

is first sucked up to prevent coagulation, then the blood, which is at once transferred to a tube containing more of the sodium citrate solution. Blood may be added to the citrate in the proportion of 1 to 5.

The citrate, by precipitating the calcium salts of the blood, effectually prevents coagulation. The citrated blood is now transferred to the centrifuge tubes and thoroughly centrifugalized. A very considerable speed —10,000 revolutions per minute—may be advantageously employed ; the corpuscles will be thrown down quickly, and yet escape damage. It is to be remembered that the white cells are lighter than the red, and will therefore be thrown down last. It is well to continue the operation till a distinct white layer is seen lying upon the layer of reds, for efficient centrifugalization means numerous white cells, and so greater facilities in counting. The clear supernatant citrate solution is pipetted off, care being taken not to disturb the white layer. Some of the 0·8 per cent. sodium chloride solution is now added to the cells, and these thoroughly mixed up with it and again thrown down. Concentration of the white cells may be effected by removing the upper layer of cells from one tube, adding these to the second tube, the lower layer in the first being then thrown away. The washing with normal saline solution is repeated once or twice. As much of the liquid as possible is finally removed ; the cells, thoroughly mingled with what is left, are then ready for use. A little plug of cotton-wool will prevent access of organisms from the air.

3. *Preparation of the Bacterial Emulsion.*—This, with one exception—that of the tubercle bacillus—has always to be prepared fresh. Young organisms stain better and more uniformly than old. It is, therefore, better to

employ as recent a culture as possible, especially in the case of such organisms as that of Morax Axenfeld, which begin to involute even before eighteen hours. A twelve- to sixteen-hour-old culture on an appropriate medium—such as agar for staphylococci, streptococci, coli, etc.; blood-agar for gonococci; nutrose ascitic agar for *Bacillus Morax-Axenfeld* or *Micrococcus catarrhalis*—is, therefore, to be employed. If the growth be a very copious one it is best to take a loopful of the culture on a platinum wire, and carefully emulsify it in a watch-glass with a little of the 0·1 per cent. NaCl solution. If the growth be scanty, then it is best to pour a few drops of the solution into the culture-tube and emulsify it *in situ*. The turbid emulsion thus produced contains many clumps, which are to be thrown down by means of the centrifuge. A minute or two will usually suffice at a high speed, but experience alone will teach just how long it should be continued. In any case, it must be efficient, for nothing is more annoying than to find clumps in the films when everything has been completed, for if accuracy be desired the whole process must then be repeated. Experience, again, alone will teach whether the emulsion requires further dilution. The opacity of an emulsion, say, of gonococcus must be much greater than that of emulsions of staphylococci or Friedlander's bacillus in order to give the same count in the normals. A strength which will give a count of about 150 to 250 bacteria in the 100 cells of the normal should be aimed at. In the instance of the tubercle bacillus an emulsion once made and found satisfactory may be preserved sealed up in capillary tubes for practically any length of time, especially if the bacteria have been killed by heating to 70° C. for one hour. When wanted, all that is necessary is thoroughly to shake up

the emulsion and give it a few sharp turns in the centrifuge to throw down any clumps which may be present.

These preliminaries over, we now take as many of the fine long-drawn capillary pipettes as there are sera to be investigated. They should be chosen of as equal bore as possible. It is advisable for them to have been sealed off at the fine extremity, plugged with cotton-wool at the other, and dry sterilized. The fine ends are cut off square by means of a file scratch, and marks made with a grease pencil about 1 centimetre from the ends. The content as far as this mark is the unit volume in each case. To the plugged ends are fitted the strong rubber teats, and each pipette is marked with a number corresponding to a serum. The rubber teat is now held between thumb and forefinger and gently compressed, the capillary end inserted into the well-mixed blood-cells, and the unit volume drawn up by slightly relaxing the pressure on the teat. Next a tiny bubble of air is allowed to enter, a second and third volume of blood-cells being drawn up in similar fashion, each separated from the next by a bubble of air. A volume of the bacillary emulsion is now drawn in, then a bubble of air ; finally, 2 volumes of the serum. We thus have in order in the pipette 3 volumes of blood-cells, 1 volume of emulsion, 2 volumes of serum, each volume being separated from the adjoining by means of a bubble of air. This is the procedure usually followed, but if the emulsion be suspected to be too thin, then 2 volumes of blood-cells, 1 volume of emulsion, and 1 of serum may be employed, or the original 1, 1, 1 of Wright. The order—cells, emulsion, serum—should, however, always be followed, for in this way contamination of the cells by the bacterial emulsion, or introduction of opsonin from the serum into the emulsion, is avoided.

By gentle pressure on the teat the several volumes are expressed on to a clean glass slide, and thoroughly mixed by alternately sucking the mixture into the pipette and squeezing it out again upon the glass slide. Only by thorough mixing can a satisfactory count be ultimately obtained. The mixture is finally withdrawn as completely as possible some little distance into the pipette, and the extremity sealed off in the flame.

This operation is repeated with each serum. The several pipettes, carefully labelled, are then placed in the incubator at 37° C. for fifteen minutes. By means of a file-scratch the ends are then cut off, the content of each blown out on to a clean glass slide, and very carefully mixed. Half the drop is then transferred to a second slide, and two blood-films prepared by the slide method—*i.e.*, by drawing the extremity of one slide held at an acute angle over the surface of the other upon which the drop of blood has been placed.

Mention may here be made of two points of some importance: Firstly, the thickness of the blood-film depends partly upon the pressure employed in the spreading, and to a greater extent upon the inclination of the moving slide to the stationary one. The more vertical the former is held the thinner the film, and, conversely, the more acute the angle the thicker the film. Now, the ideal film is one in which the corpuscles do not lie one upon the other, but are even separated by distinct intervals, for in such an one the white blood-cells flatten out, and consequently are of larger size. The contained bacteria are, therefore, much more easily distinguished after staining, and counting is consequently facilitated. Films containing tubercle bacilli may, however, be spread rather thicker than in the case of other organisms, for

the staining methods are more drastic, the organisms show up more clearly, and the red cells are practically invisible.

To obtain the best films firm pressure should, therefore, be employed, and the slides should be held at an angle of 60 degrees to one another.

Secondly, owing to their greater viscosity, the white cells tend not only to be drawn towards the end of the film, but also to run to the edges. These facts may be turned to practical advantage if the precaution be taken not to place too large a quantity of blood upon the slide. Instead of using a slide of ordinary breadth for spreading, one may be bisected longitudinally by means of a glazier's diamond, and this half slide employed. If the drop of blood be then placed at the mid-point of the breadth of the slide, but near one extremity, and the half slide used as a spreader, a film is obtained with two edges lying some little distance from the margins of the slide, and along these edges the white cells will be found collected. Next, by moving the spreader in a series of little jerks instead of with a uniform motion, a number of little valleys, as it were, are made in the film, in which the white cells collect just as they do along the edges.

Attention given to these trifling details is well repaid by the additional ease with which the slides are counted.

The films, having been spread, are then allowed to dry in the air. One of each is reserved in case of accident; the others are treated as follows: If containing tubercle bacilli, they are then fixed for fifteen minutes in methylic alcohol, or for one hour in a mixture of equal volumes of ethyl alcohol and ether, stained by the Ziehl-Neelsen method, and counterstained with toluedene blue. Five minutes' application of the latter stain, followed by

thorough washing under the tap, will show up the bodies of the white cells most effectually. For any other organism than the tubercle bacillus the films are best stained according to Leishman's method.

Next, with $\frac{1}{12}$-inch oil-immersion lens and a mechanical stage the numbers of bacteria contained in each consecutive five polymorphonuclear leucocytes are noted till 100 cells have been counted. No estimation can be considered satisfactory unless the numbers of bacteria found in each five cells approximate to each other. The following points may here be noted, and too much stress cannot possibly be laid upon their importance if accuracy be desired in the estimation : Firstly, the advisability of counting as many cells and their bacterial contents as possible. Reliance is commonly placed upon a count of fifty cells. I would maintain that no amount of care at every stage will ensure an accurate result with such a count ; 100 cells is the minimum number that should be observed. Secondly, the occurrence of bacterial clumps of any size in a film, especially if these lie upon any of the cells, should damn such a film beyond redemption. There is nothing for it but to repeat that experiment with that serum, and, of course, with a fresh normal. Thirdly, the occurrence of clumps of leucocytes, especially if these be held together by threads of fibrin, should render the experiment null and void. Once more repetition is more than advisable. Of course, both these last difficulties should not occur. They are, as a rule, the result simply of lack of care in preparing the blood-cells and the bacterial emulsion.

The determination of the index is now completed as follows : The normal serum is taken as having an opsonic index of unity. The number of bacteria found in 100

cells of each of the patients' slides divided by the number in 100 cells of the normal slide gives their respective indices. To recapitulate, then, the points of importance, by observance of which can alone be accuracy secured and much time and trouble saved ·

1. The solutions used for the preparation of the blood-cells must be quite free from hairs and filaments, for these inevitably entangle the white cells and lead to clumps in the films.

2. The blood must be received into sufficient citrate solution to ensure complete prevention of clotting, and the cells, when washing is complete, must be thoroughly mixed to ensure equal numbers of leucocytes in equal volumes.

3. The bacterial emulsions must be thoroughly centrifugalized to free them from all clumps, and growths of not more than eighteen hours should be employed for their preparation. The strength should be such that 150 to 250 bacteria are found in 100 cells of the normal.

4. The several volumes must be thoroughly mixed, both before and after incubation, to secure uniformity of count in each series of five cells.

5. The films must be spread thinly to ensure the polymorphs being as large as possible.

6. Staining must be satisfactory, and the cell body shown up. If this prove not so, the reserve slide must be stained.

7. At least 100 cells in each film should be counted.

8. If at the first attempt an unsatisfactory result is obtained, whether from clumps of cells or bacteria, or from too few white cells being present in the films, perseverance in counting imperfect films is to be deprecated. Time and temper will alike be saved by repeating the whole estimation.

Brief reference may here be made to recent attempts

at shortening the technique in determinations of tuberculo-opsonic indices by the employment of emulsions of killed organisms which have been already stained with carbol fuchsin. Although one or two observers have reported favourable results, the more general experience is that accuracy cannot be thereby secured. The chief difficulty appears to be in the preparation of a satisfactory emulsion free from clumps. Staining, whether by weak and cold or hot and strong fuchsin solutions, seems to affect the organisms in such a way that centrifugalization, which throws down the clumps, also suffices to throw down the single bacilli.

Other Methods of Estimating the Opsonic Content of the Blood.

Considerable exception has been taken, especially in America, by Simon, Lamar, and Bispham,[1] and by Walker,[2] to Wright's method as an accurate means of measuring the opsonic content of the blood. Clumps of leucocytes and of bacteria are considered to introduce a considerable error, and to be practically impossible to avoid even in the case of staphylococci. To this it may be replied that further practice on the part of these observers will enable them to overcome this insurmountable difficulty. In place of the opsonic index Simon would substitute an index obtained by diluting the blood in varying proportions (ten to thirty times), and after incubating with a bacterial emulsion of considerable strength, comparing the percentage of phagocyting leuco-

[1] *Journal of Experimental Medicine*, August, 1906, p. 651; *Ibid.*, September, 1907, p. 485.

[2] *Journal of Medical Research*, July, 1907, p. 521.

cytes in the specimen of blood under investigation with the figure obtained after a similar procedure with a specimen of normal blood. This he calls the 'percentage index,' and finds it sometimes to agree well with the opsonic index, sometimes to differ considerably from it, in which event he prefers to follow the guidance of his percentage index. Perusal of Simon's papers induces me to believe that he failed completely to master the technique of finding the opsonic index. As to the value of his index I offer no opinion.

Walker's objections appear to be much more weighty. He urges the fact that even in sera weak in opsonins there is much more than sufficient opsonin present to sensitize all the bacteria in the weak bacillary emulsions employed. Wright and Douglas's finding that normal serum may be diluted twenty-fourfold with little impairment of its opsonic power confirms this, rather than demonstrates ferment properties in opsonin. Walker estimated the rate at which bacteria are sensitized by opsonin, and found the process to be a very rapid one indeed, being practically complete in one minute even with diluted sera. Should this be true, it seems to follow that the opsonic indices of all sera should come out as unity unless they contain less than one-twenty-fourth part of the opsonin present in the normal serum. Unless, therefore, other factors than opsonization of the bacteria and phagocytic action of leucocytes be involved, a fallacy must exist somewhere in his experiments.

His proposal, however, to use strong bacillary emulsions instead of weak ones, and to dilute the sera ten- to twenty-fivefold, thereby ensuring complete utilization of all the opsonin present in the sera, and a maximum phagocytosis, is, if practicable, worthy of consideration.

Despite all these criticisms, Wright's method of determining the opsonic index holds complete sway in England, and under its guidance cases are being treated with complete success which previously were quite outside the realm of practical medicine. Considerable perfecting of other methods and evidence of their greater practical utility are required before they succeed in displacing the opsonic index method.

CHAPTER III

PREPARATION OF THE VACCINE

The general consensus of opinion is that the best possible results are, as a rule, only to be looked for when organisms isolated from the patient's own lesion are employed for the manufacture of the vaccine. Several considerations may, however, militate against the advisability of this procedure. The chief of these are as follows :

1. Where the isolation of the organism is so difficult and tedious that the resultant loss of time would fail to compensate for the advantages obtained. An excellent example of this is afforded in tubercular affections. Here we are compelled to resort to inoculation experiments, the animals usually selected for the purpose being the rabbit or guinea-pig, and the site of inoculation either the subcutaneous tissue of the groin of the latter or the anterior chamber of the eye of the former. Of these two animals, the guinea-pig is generally held to be the more susceptible to the tubercle bacillus, dying of general tuberculosis from six to ten weeks after inoculation, according to the virulence of the organism and the number introduced. On the other hand, if tuberculous material be introduced into the anterior chamber of the eye of the rabbit, an iritis which is almost pathognomonic results in from two to four weeks. In either case the loss of time is very considerable. Nor is this all. The growth of the tubercle bacillus is again so slow, and the preparation of

tuberculin so difficult an operation, that another two or three months would be consumed in the preparation of the vaccine. This is very greatly to be regretted, for many of the only partial successes or even failures in cases treated by tuberculin are possibly very largely due to the employment of stock tuberculin. This question will be again referred to later.

A second example of this class of case is afforded in some chronic gleets. The gonococcus may be visible in smears of the urethral secretion, yet, despite the utmost care in taking the cultures, it may prove impossible to free the gonococcus from the contaminating organisms.

2. The infection, although localized, may be of so acute and destructive a type that the loss of even two or three days may be of vital importance. An excellent example of this is seen in gonorrhœal conjunctivitis in the adult. Here prompt injection of a stock vaccine is obligatory immediately the patient is diagnosed. I have seen cases, so severe that total destruction of the sight was inevitable in two or three days, thereby completely held in check, and, save for the destruction which had already occurred, cured within a week (*vide* case under ' Gonorrhœal Infections ').

3. Where the infection is so very chronic that it is reasonable to suppose that the virulence of the infection has been greatly reduced, though even here it is better wherever possible to test the virulence by an inoculation experiment upon animals. Good examples of this class of case are afforded by—(*a*) very chronic cases of osteomyelitis which have been subjected to considerable surgical treatment; (*b*) chronic gonorrhœal infections, especially old gleets in the male, and tubal cases in the female.

4. A final exception may be made in the instance of such organisms as seem to be definite entities, and not to compose a family group of such closely related members as the streptococci. So far as we are aware, there is, for example, but one *Bacillus septus* and one pneumococcus; yet even here the better plan is undoubtedly the preparation of a special vaccine, unless other considerations are against the adoption of this plan.

The method employed for the isolation of the organisms will vary according as to whether we are dealing with a pure or a mixed infection, and this point may be largely determined by first making smears, staining by Gram's method and with methylene blue, and examining microscopically.

Should the infection be unmixed, then cultures are to be made at once upon the medium best suited for the growth of the organism in question, such as blood-agar in the case of pneumococcus, nutrose ascitic agar or blood-agar in the case of gonococcus, agar in the case of staphylococcus, glycerine potato in case of tubercle. If the infection be a mixed one, it must be borne in mind as a most important point that the isolation must be done as quickly and in as few subcultures as possible, for only thus is a fully virulent growth likely to be obtained. Of any peculiarities of growth of an organism in presence of others advantage is therefore to be taken, and cultures made from the infected part with every possible care.

A few details which have been found useful may here be given.

Tubercle Bacillus.

The tubercle bacillus is mentioned because the author feels convinced that more and more will it be

found advantageous in difficult cases to continue injections with a stock tuberculin only while a special one is in process of manufacture.

The peculiarity of localized tubercular affections is the paucity in the number of bacilli present. This holds true whether it is the pus from the tubercular joint or the tissues of a tubercular gland or conjunction. In the case of tubercular bladders and kidneys, however, very large numbers of bacilli may be discharged in the urine. Some means must, therefore, be adopted not only of freeing the tubercle bacilli from contaminations, but also for increasing their numbers. This is done, as said before, by inoculating a rabbit or guinea-pig. If the material be pus or solid gland, this is done directly ; if conjunctiva, care must be taken to cleanse the eye thoroughly with sterile saline before removing the piece of conjunctiva ; if pus in urine, the bacilli are to be separated by thoroughly centrifuging the urine which has been drawn off with a catheter, washed well with sterilized water, and again centrifuged, repeating this several times. The final deposit may then be employed like any other inoculum. Immediately the animal has died, or as soon as caseous glands are to be felt, or after three to four weeks in the case of injection into the anterior chamber of the eye of the rabbit, death is produced by means of chloroform ; the animal is opened with all antiseptic and aseptic precautions, and culture-tubes of glycerinized potato inseminated with as large portions of the diseased glands or iris as is possible. The tubes are then sealed up and incubated at 37° C. for six to eight weeks, when a copious growth of tubercle bacilli should be available for the manufacture of tuberculin.

Staphylococcus Albus and Aureus.

(*a*) In cases of acne, furunculosis, and sycosis, are generally present in a state of purity, but often in limited numbers. It is not, therefore, advisable to do more than wash the surface of the skin with warm soap-and-water. The pus should then be carefully expressed from a solid pustule, if possible, for the softer ones may prove sterile, and a series of two or three sloped agar-tubes inseminated with varying amounts of the pus, and incubated for twenty-four hours at 37° C. A colony may then usually be picked out and employed to plant the required cultures.

(*b*) In cases of periostitis and osteomyelitis the infection may be a mixed one, when it is perhaps advisable to mix up some of the pus with a tube of broth and use some of this, either directly or after twenty-four hours' incubation, to make a series of agar-plates, from which a colony may then be selected.

Streptococcus.

The range of utility of streptococcal vaccines will be considered later; suffice to say here that cultures may have to be obtained from pus, fibrinous exudate, or the blood. If microscope films prove the infection to be an unmixed one, cultures may be made at once upon agar; otherwise agar-plates must be made from some of the material after mixing it up with broth. I have found it highly advantageous in these cases to incubate the broth mixture for twenty-four hours at 37° C. before preparing plates. On agar streptococci grow much more slowly than other organisms, especially staphylococci,

whereas in broth this is not only not the case, but the streptococcal colonies also tend to fall to the bottom of the broth. Slight centrifugalization accentuates this tendency. The supernatant liquid may then be poured off, and agar-plates prepared from the concentrated streptococcal emulsion. A colony having thus been isolated, subcultures are to be made upon sloped agar-tubes. The growth after eighteen to twenty-four hours is so slight that several tubes must be employed. A better way is to employ agar-plates inseminated by means of a glass rod, as the surface for growth is thus greatly increased.

If cultures are to be made from the blood, it is necessary to withdraw quite a considerable quantity—about 5 c.c. —from one of the large veins in the antecubital fossa. The skin is thoroughly washed with warm soap-and-water, and then with sterilized water. A bandage is applied tightly well above the elbow. Into a 10 c.c. syringe which has been well boiled about 1 c.c. of sterilized 2 per cent. sodium citrate solution is introduced to prevent clotting in the needle. The vein is then punctured in a direction against the venous flow, when the blood will at once flow into the syringe, which can then be filled. Three culture-tubes, each containing 10 c.c. of broth, are taken. Into the first 2 c.c., into the second 1 c.c., into the third 0·5 c.c. are then introduced ; they are well shaken up and incubated at 37° C. for twenty-four hours. The blood clots in a few hours, the pigment sinking to the bottom of the tube, leaving a translucent jelly-like clot suspended in the broth. In this clot the colonies develop as isolated masses, which may be easily removed by means of a pipette and used to inseminate agar tubes or plates.

Gonococcus.

This very delicate organism may require particular care in isolation. In cases of gonorrhœal conjunctivitis it is, however, present in a state of practical purity. It is only necessary to wash the eye out with sterilized water. After waiting a few minutes, the eye being kept closed in the meanwhile, small quantities of the exudate may be taken up with a sterilized platinum loop and used to inoculate sloped tubes of blood-agar ; or, better still, plates of blood-agar may be inseminated by means of successive strokes of one or two loopfuls of the exudate. In this way distinct colonies are usually to be seen after twenty-four to thirty-six hours' incubation at 37° C. In urethral cases it is always well to take particular pains in cleansing the external meatus. The penis is held just behind the glans, the external meatus being held closed. The whole of the glans is then well cleansed with warm soap-and-water, then with weak antiseptic, finally with sterilized water. Any pus in the extremity of the urethra is then squeezed out and wiped off with damp sterile wool. The pus from further back is then expressed, received upon the platinum loop, and used to plant cultures as before. In chronic cases it may be necessary to pass the loop a little way into the urethra. It is in these cases well to remember that the larger number of cocci are to be found in the thin serous discharge rather than in the grumous. Sometimes, despite all care, numerous attempts will fail to isolate the gonococcus in very chronic cases. It only remains then to employ a stock vaccine.

A colony of pure gonococci having been isolated, fresh cultures are now to be planted. For this purpose we have the choice of two media. Freshly prepared blood-

agar made with human blood, which is thoroughly mixed up with the agar and tints it a bright red. The medium should be quite moist, and is much superior to the similar preparation made with rabbit's blood. As an alternative nutrose ascitic agar is slightly inferior, but distinctly valuable. It consists of 2 per cent. agar, to which an equal bulk of ascitic fluid is added, and 2 per cent. nutrose. It is somewhat difficult to prepare, owing to the insolubility of the nutrose. Once made, however, it keeps very well. Personally, I now always use human blood-agar. The cultures are incubated at 37° C. for twenty-four hours.

Pneumococcus

also grows best on human blood-agar. If successive strokes be made either upon blood-agar slopes or plates, a pure culture can usually be obtained at the first attempt, especially from an empyema or otitis media, and in eye cases if the eye has been well washed out previously with sterilized saline. In pneumococcal endocarditis cultures must be made from the blood in exactly the same way as described for streptococci, with the additional insemination of a tube of agar, by allowing a few drops of the blood to run over its sloped surface. From sputum its recovery is more difficult, and is best done by inserting a small piece of sputum, which has been well washed several times in sterile saline solution, under the skin of a rabbit or mouse. In about forty-eight hours the animal will die with numerous capsulated cocci throughout its blood. Some of the heart blood is then taken, with aseptic precautions, and allowed to run over the surface of tubes of sloped agar. In twenty-four hours numerous small transparent colonies, like drops of dew, appear.

So rapidly does this organism lose its virulence, and therefore its value for the preparation of a vaccine, that even in four or five days after isolation from an animal's body its pathogenicity is already diminished. It is, therefore, especially necessary in the case of this organism that a first subculture should be employed for a vaccine. As in the case of the gonoccocus, the cultures should be made on human blood-agar and incubated for between eighteen and twenty-four hours at 37° C.

Bacillus Coli Communis

may be present in a state of purity in appendical and extraperitoneal abscesses, in suppuration round the bile-ducts, in endocarditis, abscesses around the kidneys, and in the Fallopian tubes. It also occurs as a mixed infection in inflammation of the urinary passages, cystitis, and pyelitis. Its isolation is a very easy matter by means of agar, or, better still, plates of McConkey's medium (2 per cent. agar, containing 2 per cent. dextrose coloured by neutral litmus). Inasmuch as the *Bacillus coli* ferments dextrose with acid formation, the colonies of that organism will turn the litmus red, and may be picked out more easily (despite the fact that, of course, numerous other organisms also ferment dextrose with formation of acid). Subcultures are then to be made on agar-slopes.

Bacillus of Friedlander.

This organism is especially easy of isolation, as it appears to have the power of inhibiting the growth of almost all other organisms with which it may be admixed. For instance, if equal numbers of *Staphylococcus albus*

and bacillus of Friedlander be introduced, each separately, into a tube containing equal volumes of broth, and incubated at 37° C. for twelve hours, equal numbers approximately of each organism will be found in equal volumes of the cultures; but if the two organisms be introduced into one tube of broth in the ratio of 1,000 staphylococci to 1 bacillus of Friedlander, and incubated at 37° C. for twelve hours, the ratio found will be hundreds of thousands of the latter to one of the former.

Whatever the material may be, pus or nasal mucus, all that is necessary, then, is to mix up a little of the material in a tube of broth, incubate for eight hours, and then make agar-plates in the usual manner. Colonies of the bacillus of Friedlander will be found to have attained a considerable size—$\frac{1}{8}$ inch, say, in diameter—after twenty-four hours' incubation, and from one of these agar-tubes may be inseminated.

The Bacillus Septus or Coryzæ Segmentosus.

This organism may also readily be isolated from nasal or pharyngeal mucus by mixing a little of it up in sterile saline or broth, and from this emulsion preparing agar-plates. Twenty-four hours' incubation at 37° C. will result in the appearance of colonies of considerable size, from which agar-slopes may be inseminated.

Differentiation of this organism from the other members of the diphtheria group is necessary. In microscopical appearance it differs somewhat from all the others. It is a short, rather thick bacillus, with rounded ends, one of which is usually larger than the other. In twenty-four-hour-old cultures it may be so short as to resemble an oval coccus. By the third day a very characteristic

appearance is to be seen. The protoplasm of the ends of the bacillus is deeply stained, leaving an unstained band or septum across the middle, hence the name. Involution forms are uncommon and not pronounced, while polar granules are not revealed by Neisser's method of staining.

Gordon considers that the reactions in neutral litmus peptone broth to which 1 per cent. of glucose, lactose, saccharose, and maltose have been respectively added, serves to differentiate this organism completely from the *Bacillus diphtheriæ* on one hand, and from Xerosis and Hoffmann's bacillus on the other. In the case of the *Bacillus septus* there is a tendency to acid formation in all four carbohydrate media, which may not be observed till later than the third day. The *Bacillus diphtheriæ* produces a strongly acid reaction in glucose broth even before three days, while in the cases of Xerosis and Hoffmann's bacillus an alkaline reaction is produced in all four media.

The *Bacillus diphtheriæ* is alone pathogenic to animals.

The Micrococcus Catarrhalis

is best isolated from nasal or pharyngeal mucus by making a succession of stroke cultures on blood-serum or blood-agar plates. The organism is rather like the gonococcus in microscopical appearance, but differs from it in showing considerable variation in size, and also in the fact that the larger-sized organisms tend to retain the stain by Gram's method unless decolorisation be very thoroughly carried out. In cultural activities it also differs sometimes, growing feebly on gelatine, and also in forming a typical growth in broth. This consists

in the formation after two or three days, if undisturbed, of a gelatinous-looking sphere near the bottom of the broth, covered with small spines, giving it a sea-urchin appearance. Subcultures are best made on blood-agar or on nutrose ascitic agar.

It must, however, be noted that other cocci are to be found in nasal and tracheal mucus which closely resemble the *Micrococcus catarrhalis*, and, like it, fail to retain the stain by Gram's method. Differentiation of these catarrhalis-like organisms from the true *Micrococcus catarrhalis* is by no means easy, but the following points are of service :

1. The *Micrococcus catarrhalis* grows in pairs or tetrads, never in chains, like some of the others.

2. It does not produce acid in broth cultures containing glucose, saccharose, maltose, or galactose, whereas some of the others ferment one or more of these sugars.

3. The cocci of the pseudo-catarrhalis group are, as a rule, smaller and more uniform in size and staining reaction.

Morax-Axenfeld Bacillus, or Bacillus Lacunatus.

The isolation of this organism is best carried out in cases of chronic conjunctivitis by taking up some of the thin serous secretion from near the caruncle, and making successive strokes on tubes of blood-serum. After twenty-four or thirty-six hours' incubation characteristic areas of liquefaction of the blood-serum will be evident.

If films be prepared from the bottom of one of these, the typical non-Gram staining diplobacillus will be seen already beginning to involute. A pure colony having been found, tubes of nutrose ascitic agar are now to be

inseminated. Inasmuch as this organism begins to involute in from eighteen to twenty-four hours and growth is but feeble (one tube yielding under favourable circumstances but five or six doses), a considerable number of tubes must be employed if any quantity of vaccine be desired.

The Diplococcus Intracellularis (Weichselbaum), or Meningococcus

in cases of cerebro-spinal meningitis is best isolated from the cerebro-spinal fluid obtained by lumbar puncture. A pure growth is obtained by planting this upon agar or blood-serum, where it forms a number of transparent colonies, which run together to form a thin layer. If cerebro-spinal fluid be not obtainable, then isolation must be attempted from the nasal secretion from as high up on the septum and turbinal bones as is possible by means of the platinum loop. Subcultures are best made on blood-serum. In these cases careful differentiation from the *Micrococcus catarrhalis* and pseudo-catarrhalis cocci so commonly present in nasal mucus is necessary. The points given in table on p. 51 are of great service.

PREPARATION OF THE EMULSION.

Having thus obtained a pure eighteen- to twenty-four-hours-old growth of the organism on the suitable medium, we now proceed as follows (the tubercle bacillus alone excepted): The following are the necessary materials: Platinum loop; 0·1 per cent. solution of sodium chloride in distilled water, sterilized by boiling; two small strong Ehrlenmeyer flasks, and three or four small glass beads,

TABLE VI

Diplococcus Intracellularis.	Micrococcus Catarrhalis.
I. Colonies on agar soft and sticky, smooth, or only finely granular, confluent only when crowded.	I. Colonies on agar thicker, more opaque, coarsely granular, readily becoming confluent, and of firm consistency.
II. Cultures in broth are generally turbid.	II. Cultures in broth usually remain clear, with a coarsely granular deposit at the bottom, usually suspended in a mucus-like ball.
III. Produces acid from maltose, and usually from glucose, galactose, and levulose, but not from saccharose.	III. Does not produce acid from any of these carbohydrates.
IV. Does not agglutinate spontaneously in emulsions, but does with the serum of an animal which has been injected with the meningococcus.	IV. Agglutinates spontaneously in emulsions even of considerable dilution.

also sterilized ; a centrifuge with 10 c.c. centrifuge tubes ; a sterilizer which can be maintained at any temperature between 55° and 65° C. for one to two hours ; tricresol ; a capillary pipette, with rubber teat ; some sterilized solution of 2 per cent. neutral sodium citrate in distilled water ; four glass slides ; Leishman's stain ; distilled water ; microscope with $\frac{1}{12}$-inch oil-immersion lens and mechanical stage.

If the culture tube do not contain sufficient water of condensation, 4 or 5 drops of the 0·1 per cent. saline

solution are now introduced. By means of the platinum loop the bacterial growth is emulsified as thoroughly as possible.

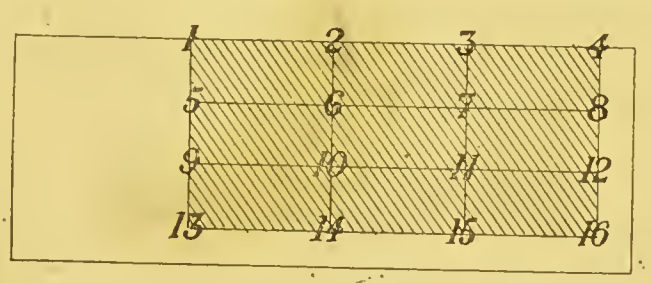
The two or three tubes are treated in this way, a little more saline added, and the whole transferred to the small flask, with two or three glass beads. The tubes are washed out with a few drops of saline, which is added to the first portions. The emulsification of the growth is now completed by agitating the flask for some minutes, the beads helping to break up the colonies present. The emulsion, which should measure about 5 c.c., is now transferred to one of the centrifuge tubes, an equal volume of water being added to the other as counterpoise. After a few minutes' more or less vigorous centrifugalization, according to the size of the organism, the emulsion is poured off from the sediment into the second flask, and is ready for standardization.

Standardization of the Vaccine.

This is carried out as follows: One end of a few inches of glass-tubing, $\frac{3}{8}$ inch in external diameter, is drawn out into a fine capillary thread, which is then cut off, giving a total length of 6 to 8 inches. A rubber teat is fitted to the larger extremity, and a mark made upon the capillary thread about $\frac{1}{2}$ inch from the end. This constitutes the unit volume. The emulsion being ready to hand, the finger-tip is pricked on the dorsum, and a drop of blood expressed. By gently compressing the rubber teat, and then slightly releasing the pressure, four or five volumes of the 2 per cent. citrate solution are sucked into the capillary thread; then a small bubble of air, next a volume of blood, then a bubble of air, finally a volume

of the emulsion. The whole is then expelled on one of the clean glass slides, and carefully mixed by alternately sucking it up and expelling it upon the slide. This mixing having been thoroughly carried out, the whole is divided into approximately three parts, which are transferred each to a clean slide, and then carefully and evenly spread by means of the edge of another. In this way uniform smears are obtained. These are allowed to dry in the air, and then stained with Leishman's stain for five minutes. The slides are then flooded with distilled water, which is allowed to remain for fifteen minutes ; they are then washed in distilled water till pink in colour, and no more blue escapes into the water, and dried with filter-paper.

They are now ready for counting. By means of a blue grease pencil the two diameters at right angles are marked upon the ocular of the microscope so that the field is divided into four quadrants. The counting is thereby greatly facilitated, and is carried out as follows : The smear in the slide is mentally divided up into nine equal areas, as in the adjoined figure. A whole field of the microscope is then counted at each of the angles as indicated, so that a total of sixteen fields is counted. The numbers of red blood-cells seen in each field are set down in one vertical column, the numbers of organisms in another. Each column is then added up, so that the numbers of corpuscles and bacilli respectively in sixteen microscope fields



are estimated. This is repeated for the second slide, and the two results added together. These thirty-two fields may be assumed to give a sufficiently accurate count. We will assume that 600 red cells have been counted and 1,500 bacilli. Now, a cubic millimetre of blood contains 5,500,000 red cells, and equal volumes of blood and of emulsion were taken. A cubic millimetre of the emulsion, therefore, contains $\frac{5,500,000 \times 1,500}{600}$, or 13,750,000 organisms per cubic millimetre, or 13,750,000,000 per cubic centimetre.

It being desirable to have doses of 125, 250, 500, and 1,000 million bacilli respectively contained in either $\frac{1}{2}$ c.c. or 1 c.c. of fluid, it now becomes necessary to dilute the emulsion. To obtain 1,000 million per c.c. it is obvious that each 1 c.c. of the emulsion has to be made up to 13·75 c.c. with 0·1 sterile salt solution. This is accordingly done, and sufficient tricresol added to make a 0·2 per cent. solution. This is of sufficient strength to inhibit the growth of, or even destroy, any spores of air organisms which may have gained admittance to the emulsion, and may escape destruction in the subsequent sterilization.

Sterilization of Vaccine.

The flask containing the emulsion is now placed in a sterilizer at 56° C. to 60° C., and maintained at that temperature for one or one and a half hours, according to the resistance of the organism to heat. The lower the temperature that can be employed with safety, the more potent is the vaccine. It is then allowed to cool, and is ready for the next step.

Tubing the Vaccine.

Materials required: Sufficient sterilized glass serum-bulbs of 1·5 to 2·0 c.c. capacity, in two colours—say white and blue; a standard burette, also sterilized and graduated to $\frac{1}{10}$ c.c.; a hypodermic needle and 2 or 3 inches of thin rubber-tubing, also sterile. To the end of the burette the needle is attached by means of rubber-tubing. The burette being set up vertically, the tap is closed and the emulsion poured in; the tap is then opened till a drop of fluid appears. Into a number of the white bulbs 1 c.c. of emulsion is run, into others $\frac{1}{2}$ c.c. The former will thus contain 1,000 and the latter 500 million organisms. The ends are sealed off by holding in the tip of the flame of a Bunsen burner. A sufficiency of these doses having been made, the remainder of the emulsion is returned in its flask, and 3 volumes of 0·1 saline solution, together with sufficient tricresol to make it up to 0·2 per cent., added. This having been thoroughly shaken up, tubing into the blue bulbs is carried out as before. One c.c. will now contain 250 and $\frac{1}{2}$ c.c. 125 million organisms. We are, therefore, in a position to administer doses of 125 millions and any of its multiples.

The bulbs are set aside till next day, when sterilization at 60° C. is again carried out for one hour. These two sterilizations should be quite sufficient to kill the organisms. Should there be any doubt, however, a third sterilization may be carried out on the following day, but is not to be recommended, as the strength of the vaccine may be impaired by too prolonged heating.

The bulbs should now be marked by means of a diamond

pencil with the name of the organism and the number contained in each tube. In this way mistakes at any subsequent date will be obviated.

The Various Forms of Tuberculin.

Tuberculin T. (*Koch*, 1890)

is a clear brownish fluid, obtained by filtering through a porcelain filter a glycerine broth culture of tubercle bacilli which has been evaporated on a water-bath to one-tenth its volume.

Tuberculin T.R. (*Koch*).

Young, highly virulent bacilli are dried *in vacuo*, and then comminuted by machinery. The dust thus obtained is heated with distilled water, and the mixture placed in a centrifuge, making 4,000 revolutions per minute. In this way an opalescent fluid (T.O.), possessing analogous properties to the old tuberculin, and a deposit are obtained. The latter is then emulsified with successive quantities of water, and constitutes the new tuberculin, or T.R., which is sold in bottles containing 10[1] milligrammes of solid bacterial substance per c.c.

The occasional presence of living tubercle bacilli capable of multiplication in the new tuberculin has led to occasional accidents. Wright and Douglas found that heating to 60° C. for one hour sufficed to kill any

[1] This, owing to a mistake on the part of the makers, is erroneous. It would appear to contain only 2 milligrammes of solid substance per c.c. The doses indicated, not only in these pages but in all the publications by other authors who have employed Koch's T.R., require division by 5 to render them accurate.

bacteria, and did not impair the tuberculin. After tubing off into appropriate doses, it is, therefore, well to thus sterilize the tuberculin before administration.

Inasmuch as the T.O. thus obtained gives no precipitate with glycerine, while the T.R. does, it is held that the former contains those elements of the bacilli which are soluble in glycerine, and are therefore similar to those contained in the old tuberculin. The T.R., on the other hand, is supposed to be freed from these dangerous constituents. All the immunizing substances of the T.O., according to Koch, are contained in the T.R., and a man immunized with T.R. will not react against a large dose of T.O.

Tuberculocidin (*Klebs*).

Klebs, in 1891, came to the conclusion that the deleterious substances contained in T.O. were of an alkaloidal nature. These he endeavoured to remove, and to the tuberculin thus obtained gave the above name.

Tuberculosetoxin (*Maksutow*).

Maksutow, in 1897, raised the objection to tuberculin that it was prepared from bacilli grown on artificial culture media, and that the chemical constituents of these media and their disintegration products introduced a complicating factor. A toxin so obtained he held was not necessarily identical with the specific toxin of the bacillus. He therefore made extracts from the tuberculous tissues of diseased guinea-pigs, and from this material obtained a tuberculosetoxin free from bacilli, and capable of producing immunity in animals in about three months.

Tuberculol.

Landman, in 1898, described a preparation in which the bacilli were extracted with normal saline solution, distilled water, and glycerine at progressively increasing temperatures, the first extraction being made at 40° C., the last at 100° C., the different extracts being then added together. To this preparation he gave the name 'tuberculol.'

Bouchard, at the International Congress of Tuberculosis, 1905, also described a new form of tuberculin, which he claimed to be bactericidal *in vitro*, and immunizing and curative in man and animals.

Tulase (*Behring*, 1905)

contains the somatic substance of the tubercle bacillus, which takes up the stain by the Gram and Ziehl-Neelsen methods. The method of preparation is a very complicated one, consisting partly in the treatment of the bacilli with chloral. It may be administered intravenously, subcutaneously, or by the mouth, and is claimed to produce both antituberculous immunity and hypersensibility to Koch's tuberculin. In persons not infected by tubercle immunization by tulase is said to be produced after four months, whereas in those already infected response appears to be more rapid.

Preparation of Combined Vaccines.

In certain conditions, such as pulmonary phthisis, tuberculosis of the bladder and kidneys, and bones and joints, additional gravity is added to the case when to the primary infection secondary ones are added. All are familiar with the comparative ease with which a case of early pulmonary phthisis or tubercular joint disease

yields to appropriate treatment, and the difficulty of dealing with such a case when once staphylococci or streptococci have complicated the infection. Occasionally, it is true, great improvement follows the administration of tuberculin alone, but the best results will, I am convinced, be secured by either previously or simultaneously attacking the secondary infection. In these instances it is, as a rule, easy to ascertain the exact nature of this infection. In bladders and kidneys it is usually the *Bacillus coli communis*, in bones and joints staphylococci or streptococci. Other forms of bacillary infection there are, however, such as Pyorrhœa Alveolaris, Gleet, and Chronic Tracheal Catarrh, in which it is wellnigh impossible to tell which out of the many different bacteria present are responsible for the condition. The only thing then to do is to employ a 'combined vaccine.' Details of cases and results will be found later. At present attention will be confined to the method of preparing such a vaccine. The first step is to take smears of the discharge. If this be sputum, suitable lumps should be chosen, and washed repeatedly in sterile salt solution before spreading the films. These are then stained with methylene blue and by Gram's method, using neutral red as counterstain. Careful note is made of the organisms present as far as possible, and their relative numbers estimated. Cultures upon suitable media—best upon several, such as upon agar, blood-agar, and blood-serum, and in broth—are also made, and films prepared from these after four, eight, twelve, eighteen, and twenty-four hours incubation, and stained as before. The identification of the various organisms is thus made more complete, and the medium upon which the relative proportions of the organisms detected in the secretion is

best preserved noted, as well as the appropriate time of incubation. Sometimes it will be found that one of the organisms most numerous in the original smears refuses to grow in the presence of the others. There is then nothing for it but to plate out cultures, isolate the various bacteria, make fresh cultures, and prepare the several vaccines separately, and then mix them together. As a rule, however, this is unnecessary. There is nearly always one medium and a certain duration of incubation which will give an emulsion in which the bacteria are preserved in approximately their original proportions. If one organism be found to outgrow the others, sufficient of it may usually be removed from colonies by means of the platinum loop to re-establish the desired ratio.

It must, however, be admitted that the best and most scientific method is to plate out cultures, isolate the several organisms, omitting any non-pathogenic air organisms which may be present, and from subcultures to prepare the several emulsions, which may be then standardized and mixed in such proportions that the appropriate initial dose of each is secured in $\frac{1}{2}$ c.c. of the mixture.

The usual result of two or three injections at three-weekly intervals of such a vaccine is to produce a most marked reduction in the number and variety of the organisms to be seen in films prepared from the secretion. These may then be dealt with by a fresh vaccine prepared in a similar manner.

Administration of the Vaccine.

The opsonic index having been taken and the suitability of the case for injection determined, the dosage

must be decided on. The average initial dose for each organism is given in subsequent pages; it is better to err on the side of too small rather than on that of too large dosage. The best site for injection is in the loose subcutaneous tissue of the side. It may, however, be done in the back or upper arm. Several little points are to be noted: thus, no one can predict how much local reaction may result. In flabby abdominal walls there is usually none. Five or six injections may produce none whatever, and the next quite a considerable amount. A small lump as large as a walnut may be formed, and the skin reddened. This may be quite painful each time the patient breathes, or coughs, or moves the abdominal wall. This result being possible, it is necessary to provide against it, and the following rules are useful: (1) Do not inject on the side upon which the patient lies; (2) in women do not inject where corsets are likely to press; (3) avoid veins, and so production of a hæmatoma; (4) do not inject so far forwards that any swelling will lie over the edge of the rectus abdominis muscle; (5) remember that if a large fold of skin be picked up and the needle be pushed well in, the inoculum will lie, perhaps, 2 inches from the site of puncture.

A very safe situation is, therefore, on the right abdomen, about $\frac{1}{2}$ inch above the anterior superior spine of the ilium, and about $\frac{1}{2}$ inch internal to it. If a good fold of skin be raised and the puncture made at the spot indicated, the inoculum will lie $1\frac{1}{2}$ to 2 inches internal to the anterior superior spine, and any reaction will cause a minimum of discomfort.

The site, then, having been decided upon, the adjacent skin should be well cleansed with warm soap-and-water,

followed by a little 2 per cent. lysol. The neck of the bulb is scratched with a file and broken off. The inoculum is then sucked up into an ordinary hypodermic syringe, which has been thoroughly sterilized. Any air-bubbles are expelled, and the needle inserted to nearly its full length into the fold of skin and the vaccine expelled. The puncture is then closed with a little collodion. These aseptic precautions may be considered hardly necessary, but infection from the skin or a dirty needle has been known to occur. Such an accident tends to discredit opsonic treatment in the minds of the ignorant public, who at once class the proceeding with Jennerian vaccination. No care is too great to take to obviate such an unhappy result.

CHAPTER IV

THE OPSONIC INDEX IN HEALTH AND DISEASE: ITS DIAGNOSTIC AND PROGNOSTIC VALUE

A. In Health.

Bulloch determined the indices towards the tubercle bacillus of forty-four medical students and forty hospital nurses, all presumably free from tubercular infection. The results showed a variation from a minimum of 0·8 to a maximum of 1·2 as compared with an index of unity for the serum of himself. The average for the whole eighty-four cases was 0·96. Urwick in twenty cases obtained an average of 1·006, and Lawson and Stewart in twenty-five cases an average of 1·0.

The tuberculo-opsonic index of the average healthy individual should therefore lie between 0·8 and 1·2, approximating as closely as possible to 1·0.

The mean staphylococcal opsonic index of twenty-five healthy adults was found by Bulloch to be 1·0; other observers have obtained a like result, the variation being, as a rule, less than in the case of the tubercle bacillus. Numerous observations with other organisms show that the same holds true in each case; it may therefore be assumed that the opsonic index for any organism of the serum of the average healthy person varies only between narrow limits, the minimum being 0·8 and the maximum 1·2.

The index has also been shown by Urwick to be practically constant from day to day in healthy subjects. He gives the following figures for the tuberculo-opsonic indices of the serum of a healthy individual as compared with his own on various dates :

TABLE VII

November	1	=	1·1	December	5	=	0·9
,,	8	=	1·0	,,	8	=	0·9
,,	12	=	1·0	,,	13	=	1·0
,,	30	=	1·15	,,	14	=	1·0
				,,	19	=	1·0

Certain factors do, however, produce very slight changes in the index. French, for instance, has found that vigorous exercise, such as a twelve-mile walk undertaken by a healthy person of sedentary habit will sometimes cause a rise from 1·0 to 1·2 or 1·3 on the following day. Ellett[1] showed that this positive phase was preceded by a negative one. I myself have noticed a diurnal variation very similar to that exhibited by the temperature chart. This is well seen in the following table, the organism employed being the bacillus of Friedlander.

TABLE VIII

Date.	8 a.m.	9 a.m.	11 a.m.	4 p.m.	12 midnt.	3 a.m.
May 15, 1906 ..	1	1·06	1·14	—	—	—
May 18, 1906 ..	1	1·11	1·20	—	—	—
May 29, 1906 ..	1	1·08	1·08	1·2	1·26	—
June 6, 1906 ..	1	—	1·07	—	1·18	1·0
June 12, 1906 ..	1	1·10	—	—	1·14	—

[1] *British Medical Journal*, July 21, 1907.

From this it would appear that the index is at a maximum between 4 p.m. and midnight, being raised by the active processes of life, a fall to unity rapidly occurring after retirement to bed. Abstinence from food or excessive exercise did not appear to have any immediate effect in the production of a lowered index.

B. In Disease.

1. *In Tubercular Infections.*—Wright, in his earlier experiments upon localized tubercular infections, found a general lowering of the opsonic index below unity. In a series of seventeen cases, exclusive of pulmonary phthisis, he found variations from 0·4 to 0·85, with an average for the seventeen of 0·64.

Bulloch investigated the indices of 150 sufferers from lupus in all stages, from very mild cases to old intractable ones of even forty years' standing. Seventy-five per cent. of the cases had indices below 0·8, while the average for the 150 cases was 0·75, distributed as follows :

TABLE IX

Opsonic Index.	Number of Cases.	Percentage.
Between 0·2 and 0·3	3	2·0
,, 0·3 ,, 0·4	3	2·0
,, 0·4 ,, 0·5	21	14·0
,, 0·5 ,, 0·6	29	19·6
,, 0·6 ,, 0·7	33	22·0
,, 0·7 ,, 0·8	22	14·8
,, 0·8 ,, 0·9	18	12·0
,, 0·9 ,, 1·0	7	4·6
,, 1·0 ,, 1·4	14	9·3

In chronic cases of surgical tuberculosis, such as of the joints, kidneys, bladder, or glands, it appears to be generally low, an average of 0·6 being obtained by Bulloch in eleven cases, and of 0·8 in nine cases by French.

Lawson and Stewart made between 2,000 and 3,000 observations upon cases of apyrexial phthisis, and found the index to be always below 1·0, varying from 0·5 to 1·0.

Urwick examined thirty-three cases of pulmonary tuberculosis in all stages. In twenty-five he found an index above 1·0, even as high as 2·6 ; in seven an index below 1·0 ; and in one case the index was 1·0.

Effect of Exercise upon Tuberculo-opsonic Index in Cases of Phthisis.

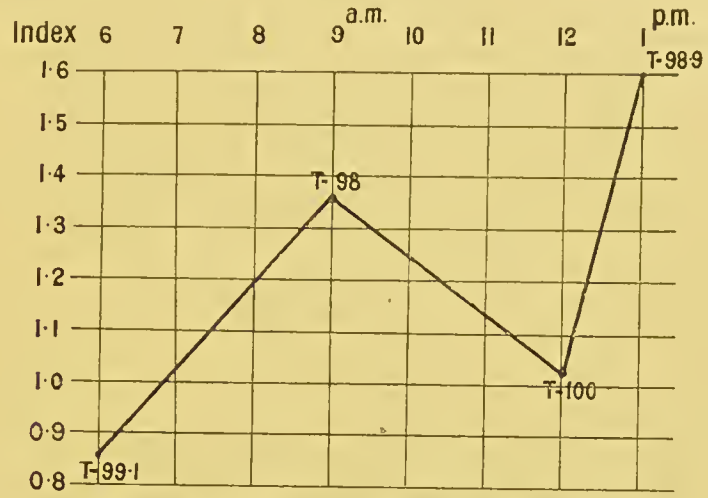
These variable results were explained by Meakin and Wheeler,[1] who studied the index at various times of the day in tubercular patients who were undergoing sanatorium treatment, some of whom were taking walking exercise and others not ; specimens of blood were taken at 6 a.m., 9 a.m., noon, and 1 p.m. If the patient was capable of taking exercise, this was done between 9 a.m. and noon ; between noon and 1 p.m. rest was taken in a long chair.

The results of some of their observations—five upon patients taking exercise and three not—are shown in the adjoined charts.

[1] *British Medical Journal*, November 25, 1905, p. 1396.

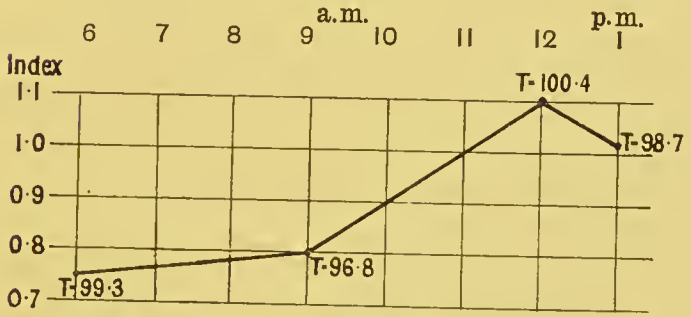
MEAKIN AND WHEELER. WALKING CASES.

CHART II



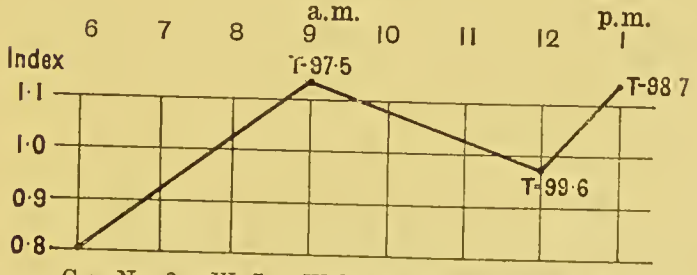
Case No. 1. Walking. September 18.

CHART III



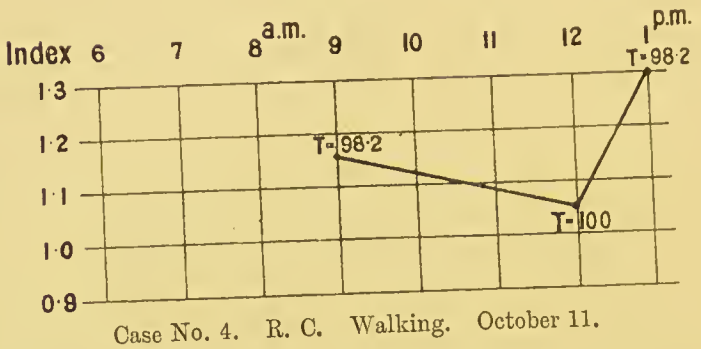
Case No. 2. C. T. Walking. September 27.

CHART IV



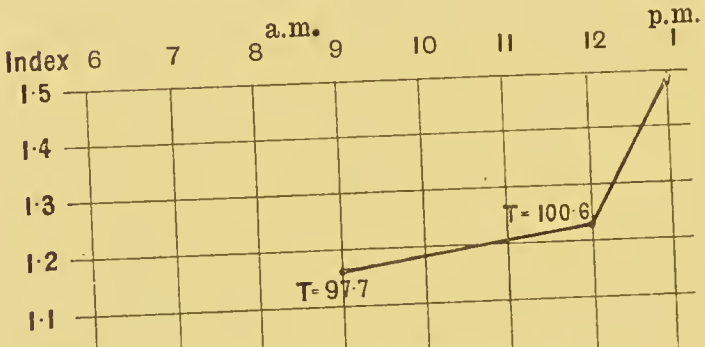
Case No. 3. W. L. Walking. September 28, 29.

CHART V



Case No. 4. R. C. Walking. October 11.

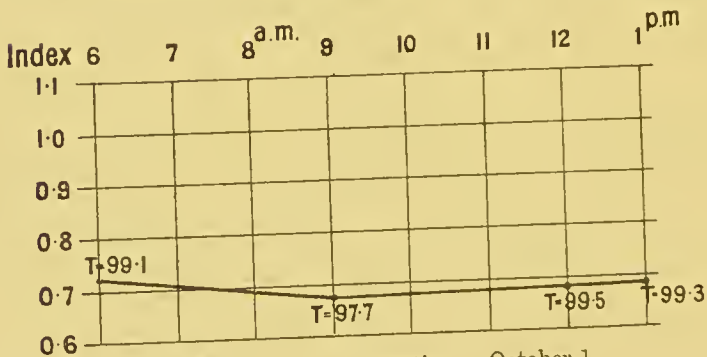
CHART VI



Case No. 5. H. M. Walking. September 16.

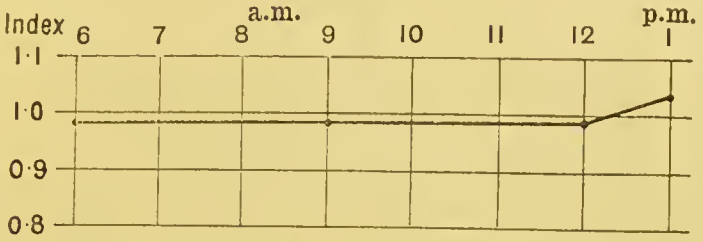
MEAKIN AND WHEELER. RESTING CASES.

CHART VII



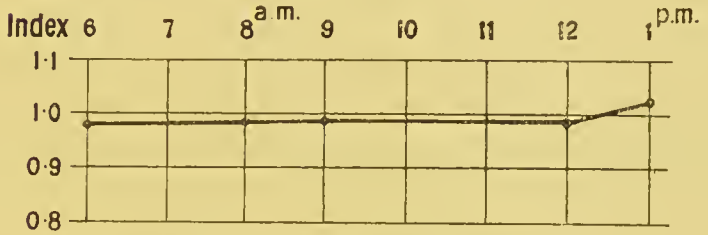
Case No. 5. H. M. Resting October 1.

CHART VIII



Case No. 6. H. B. Resting. September 18.

CHART IX



Case No. 7. D. H. Resting. October 4.

It will be observed that in all the walking cases except one a much higher index was recorded at 1 p.m. than at 9 a.m., and that this rise bears no obvious relation to rise of temperature, whereas in resting cases the index is practically constant, and either at or below unity throughout the day. This is taken to indicate that in walking cases there occurs a process of auto-inoculation by absorption of extremely minute doses of tubercular toxin by the very vascular lung tissue. How minute the dose is the shortness of the negative phase (two or three hours) clearly indicates. The process thus exactly resembles the succession of negative and positive phases which, as we shall see, is induced by a series of tuberculin injections.

Confirmation of this view is afforded by the like results which we shall see later are produced by surgical manipu-

lation of a tubercular joint. It would thus appear to be generally true that in pulmonary phthisis—

The index is above 1 in slight early cases.
The index is variable in acute cases.
The index is below 1 in chronic cases.

In acute cases there may be either a constant high index, where the body is making every effort to cope with the invaders and the conditions are favourable ; or fluctuating, where auto-inoculation is occurring—not, as Wright suggests, with too large or badly interspaced doses, but with infinitesimally small ones, so that negative and positive phases are alike of short duration, though full amplitude ; or, finally, it may be constantly below unity, if such auto-inoculations be prevented.

In tubercular infections of the eyeball, uncomplicated by tuberculosis elsewhere, the index is usually high. Thus, a case of tubercular iritis had an index of 1·3, a case of keratitis an index of 1·5. A third case, in which tubercular keratitis and iritis were complicated by tubercular cervical and mesenteric glands and by peritonitis, had, on the other hand, an index of 0·4. As will be mentioned later, all eye infections, whether acute or chronic, are usually attended by high opsonic index. The explanation of this is, I think, fairly obvious. The circulation of the eyeball is so poor and the infection so localized that the very minute doses of toxin absorbed act exactly like repeated injections of infinitesimally small doses of tuberculin — so small that the protective mechanism of the body is not exhausted. That chronic cases do not get well with this high index is, again, probably due to the poor circulation, and consequently to the small amount of opsonin brought to the part.

Eyre has observed that broken-down phlyctenules may be starting-points for tuberculosis of the conjunctiva, while Wright, in his earlier experiments, noticed that occasionally phlyctenules developed in patients undergoing inoculations with tuberculin. Nias and Paton[1] accordingly investigated the tuberculo-opsonic index in a series of twenty cases of early phlyctenular conjunctivitis, employing five cases of other forms of conjunctivitis as controls. They found striking variations from the normal in the indices of the cases of phlyctenular conjunctivitis, and practically normal indices in the other forms. The author has obtained similar results, but it must not be lost sight of that phlyctenules usually make their appearances in definitely tubercular subjects, and that the disturbance of the index is probably in the major part due to infected glands, lungs, bones, or joints.

The Effect of Menstruation upon the Index in Infected Cases.[2]

An important point to remember in connexion with a female infected by any organism is that menstruation produces a very marked lowering of the index to that organism—an effect which may begin a day or two before the period and persist for a day or two after ; the fall and rise, once initiated, move with great rapidity. It is, however, stated that in non-infected females there is a general depression of the opsonic index to all organisms ; this statement needs confirmation.

[1] Ophth. Trans. Soc., November 9, 1907.

[2] French. *Practitioner*, July, 1906.

The Tuberculo-opsonic Index as an Aid to Diagnosis.

It has been mentioned that the index to the tubercle bacillus of the sera of healthy subjects varies between 0·8 and 1·2. The important question now presents itself as to how we are to regard an index which does not lie within these limits. Does it mean that infection has already taken place, or merely that the person is predisposed to it ? That a low index always means the former of these alternatives is certainly not the case, as is shown by the following instance : Dr. Eyre, while directing the work of the Commission on Mediterranean fever in Malta, contracted the disease severely. After a short interval it was found that his index to the tubercle bacillus, which was known to be normal before his departure from England, was below 0·4. It remained at this low level for several weeks, and only slowly returned to normal. There never was any evidence soever of his having been infected by tubercle. A similar effect was also noticed in the case of Dr. C. Pryce Jones after contracting Malta fever.

It is probable that a low index precedes infection, and is due either to an acquired or hereditary inability to elaborate the chemical protective substances of the body. It is possible that a fall in these bacteriotropic substances, which is local and not general, will suffice to determine infection in certain cases. As we have seen, a low index is the rule in chronic localized infection ; and in any case of supposed tuberculosis where a low index is found, especially in the instance of a patient not coming from tubercular stock, and where clinical appearances are compatible with such a diagnosis, tuberculosis is highly

probable. It must not be forgotten that a depression of index may persist for a long time after an infection is supposed to have been cured. Thus, in fourteen picked cases of sanatorium 'cures' of phthisis in its early stages Bulloch[1] found indices varying between 0·4 and 0·86. Lawson and Stewart[2] examined the indices of twenty-five such cases. In five of these it was found to lie between 1·1 and 0·9; in the other twenty it was 0·8 or under. Consideration of these results, taken in conjunction with the extreme frequency with which indications of healed tuberculosis, either of bronchial glands or lungs, are found in autopsies upon those never recognized as tubercular subjects while alive, tends strongly to support West's view that all cases in which low indices, not explicable by such considerations as were noted in Chapter I., are found are instances either of cured or active tuberculosis. On the other hand, an abnormally high index—1·3 or over—is probably almost always a sign of active infection.

Reliance should not, however, be placed upon a single determination of the index; two at least are always advisable. Should these not agree, then a series should be done before a definite conclusion is arrived at. Continual variations certainly indicate active infection and a succession of auto-inoculations. *Per contra*, the non-occurrence of a high or fluctuating index in patients acutely ill is very strong evidence against a diagnosis of tuberculosis, and lends support to such alternative diagnoses as malignant disease of the lung, chronic bronchitis and emphysema, bronchiectasis, general debility, or gonorrhœal arthritis.

[1] *Lancet*, December 2, 1905, p. 1603.
[2] *Ibid.*, December 9, 1905, p. 1683.

An abnormally low index will assist in discriminating such conditions as—

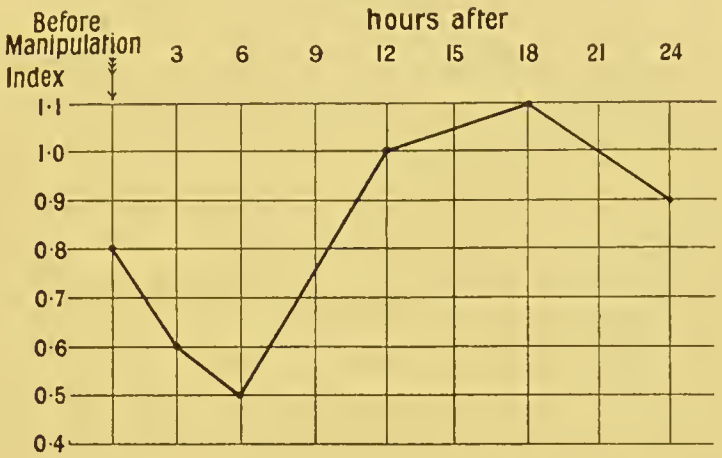
Tuberculous kidney from malignant kidney or renal calculus.
Addison's disease from pernicious anæmia.
Tubercular peritonitis from malignant peritonitis.
,, laryngitis from malignant laryngitis.
,, pleurisy from malignant and other forms of pleurisy.
,, joints from syphilitic and gonorrhœal joints.
,, adenitis from Hodgkin's disease.
,, endocarditis from fungating and other forms of endocarditis.
,, keratitis and iritis from syphilitic and rheumatic.
,, epididymorchitis from syphilitic, adenomatous, or malignant forms.
,, cystitis from that due to calculi, tumours, enlarged prostate, etc.
,, salpingitis from gonorrhœal.
,, ovary from malignant or cystic.
,, endometritis from malignant, etc.
Lupus from syphilis or rodent ulcer.

Special Methods of employing the Opsonic Index in Diagnosis.

The first method depends upon the artificial production of an auto-inoculation, and is especially applicable to tuberculosis of joints. The index is taken; passive movement of the joint is then performed by the surgeon, and fresh determinations of the index done after three, six, twelve, and twenty-four hours. Should infection not be present, minimal variations in the index will be found; but should it be present, the production of definite negative and positive phases will be evidenced. The negative phase may be fully produced within three hours or may be absent.

The adjoined chart shows the effect produced in a case of doubtful tuberculosis of the hip in a child six years old :

CHART X



Ample confirmation of the diagnosis was thus secured.

The second method is of wider applicability. A small dose of T.R. (0·0002 to 0·0004 milligramme) is given, and the index estimated daily.

In healthy subjects the negative phase, if present at all, is of very slight amplitude and short duration, lasting, as a rule, for only a few hours. The positive phase resembles the negative, and the limit of fall and rise in the index rarely exceeds 0·2 or 0·3. Lawson and Stewart[1] found no negative phase, but a rise in one instance from 1·0 to 2·1 within a few hours. In infection, on the contrary, a much more pronounced fall and rise are, as a rule, obtained ; the negative phase may last for days, or even a fortnight, and the crest of the positive phase be not attained for one to three weeks. Inasmuch as occasion-

[1] Edin. Med.-Chir. Trans., November 1, 1905. Proc. Royal Med.-Chir. Soc., November 28, 1905.

ally no negative phase is produced in cases undoubtedly tubercular, failure to obtain a negative phase does not entirely put the diagnosis of tubercle out of consideration. A third method is the employment of the original tuberculin in doses insufficient to produce the acute disturbances originally obtained. Dodds[1] reported the effect of injections of T.O. in doses containing 1 milligramme of solid substance upon the opsonic index in five doubtful cases of phthisis, and in one certain case exhibiting bacilli in the sputum. In this latter instance the index before injection was 0·7 ; twelve hours after injection of 0·5 milligramme of T.O. the index = 1·1 ; upon the fifth day it had fallen to 0·9. Of the other five cases, in four the index was normal, and remained so after injection of 1 milligramme of T.O. Of these, three were cases of old pneumococcal pleurisy, with chronic cough for months ; the fourth had a chronic cough. In the fifth case the index fell from 1·0 to 0·7, and rose next day to 1·4. He had a phthisical family history, and had had pleurisy six years previously, with persistent subsequent cough ; his sputum was streaked with blood, and occasional night sweats were present. In this case the diagnosis of phthisis was held to be confirmed.

A fourth method depends upon the fact, already noted, that in females infected by an organism the onset of menstruation initiates a very marked fall in the index towards that organism ; the cessation as pronounced a rise. If, therefore, a female be suspected of tuberculosis, determinations of the index a couple of days before the onset, towards the end of the period, and two or three days after should reveal marked negative and positive phases.

[1] *British Medical Journal*, July 7, 1906, p. 22.

In two cases of severe recurrent episcleritis, which is by some eye pathologists considered to be of tubercular origin, I utilized this method. In the first the tuberculo-opsonic index before menstruation was 0·96, and during menstruation 0·93; tuberculin injections were therefore not advised.

The second case it was 1·26 before menstruation, and 1·28 during the period. No other clinical evidence of tubercle could be found, and, as before, despite the somewhat high index, tuberculin injections were held to offer slight chance of improvement. As, however, the patient came from tubercular stock, and wished to avail herself of every chance, four injections were given at three weekly intervals, but without producing the slightest improvement. These results tend strongly to negative the idea that episcleritis has any connexion with tubercular infection.

The Tuberculo-opsonic Index as an Aid to Prognosis: A. In Pulmonary Phthisis.

It is beyond question that the cases of pulmonary phthisis which do worst are the pyrexial ones, and, as we have seen, these exhibit violent fluctuations in the index. Rest in bed steadies the temperature and opsonic index alike. The level taken up by the latter varies considerably in different cases, and sufficient evidence is not yet forthcoming to enable a definite opinion to be given as to the import of a steady high or low index.

Taking into consideration the facts that chronicity is always accompanied by a low index, and that the aim of therapeutic injections is to raise the index to or above unity, it would appear rational to assume that those cases will do best which settle down to a steady index of

1 or over, while those that settle down to an index below 1 will go on to chronicity. Meakin and Wheeler support this view. They find that the case with an index much below 1 is the case that becomes chronic, that recovers to a certain extent, but can only maintain that degree of recovery while living under sanatorium treatment; that the case, on the other hand, which during treatment shows a steady index of 1 or over is the one which makes a complete recovery if favourable conditions are maintained for a sufficient time. They lay especial stress on the statement that it is only to patients actually undergoing sanatorium treatment that this opinion applies.

Lawson and Stewart[1] took the indices of twenty-five cases of sanatorium 'cures.' In five of these it was found to be between 1·1 and 0·9; in the other twenty it was 0·8 or under.

In thirty other similar cases fourteen had indices between 0·5 and 0·9, and of these thirty cases twenty-nine had been carrying on their usual occupations, in most instances in towns, for periods ranging from six months to four and a half years, and enjoying perfect health.

As to the liability of cases with low indices to relapse, nothing definite is at present known, but authorities agree upon the distinct advisability of artificially raising to unity or over the indices in all such cases. The cases which seem to profit most when tuberculin injections are added to the other therapeutic measures adopted at sanatoria appear to be those with initially low indices, although improvement is also noticeable in those with indices above unity (see also p. 96).

[1] *Lancet*, December 9, 1905, p. 1683.

B. In Other Tubercular Affections.

Lupus.—Bulloch's experience is that the cases which do best with Finsen light are those with indices either beyond or within the normal limits; those with indices below 0·8 do worst, whereas, *per contra*, those cases which profit most from tuberculin injections are those of the latter class. Wright finds that in those varieties of lupus where the infected skin is dry and scaly, so-called lupus psoriasis, tuberculin is of little avail; while in suppurating lupus, where mixed infection by the *Staphylococcus albus* is present, good results can often only be achieved by a simultaneous attack upon the secondary infection.

As regards other tubercular affections, such as those of glands, peritoneum, joints, kidneys, and bladder, no definite rules can be laid down beyond the general statement that if tuberculin injections are not to be given, the cases that have a steadily high index do best, while those with fluctuating indices do badly, and those with subnormal indices show little tendency to recover. These last show the relatively greatest improvement under a course of tuberculin, but as experience increases it becomes more and more difficult to draw the line between suitable and unsuitable cases for such treatment, for some cases which have seemed the most hopeless have yet done well. In four cases of tubercular peritonitis which relapsed White found subnormal indices; in one which recovered, an index above normal.

CHAPTER V

SCOPE FOR THE EMPLOYMENT OF TUBERCULIN, AND SOME GENERAL RULES FOR THE MANAGEMENT OF TUBERCULAR CASES

Before discussing the management of tubercular cases it is obviously necessary to consider the nature of such infections and the manner in which the body reacts to them. The body has at its command various mechanisms whereby to cope with bacterial invasion ; these are called into play upon all such occasions. Should the means at its disposal be sufficient, the body wins the day ; should they be insufficient and ill-directed, then the bacteria gain the upper hand. Among these fighting forces is preopsonin or opsonins. Wright considers that bacterial invasion occurs in a region of lowered bacteriotropic pressure—*i.e.*, in a region where the antibacterial substances are either absent or, at any rate, reduced in amount.

Watson Cheyne disputes this, pointing out that tubercle very often establishes itself in parts which are particularly highly vascularized, instancing the juxta-epiphyseal line in bones, the nose and the face ; he therefore holds that there are many other factors, especially local factors, which are of importance.

Wright, I take it, will hardly deny this contention, but, as I have shown, opsonins are of local formation, being

brought from, not to, a part by means of the blood-stream, any condition which will affect this local formation of opsonin will therefore lower the bacteriotropic pressure at that part, and conduce to bacterial infection. Again, as Hektoen and Ruediger have shown (*vide supra*), there are many substances which are specific or non-specific antiopsonins, and the accumulation of such an one at any part will obviously predispose to local infection. Treatment must therefore be directed towards increasing the amount of opsonin formed either locally or generally, and especially to increasing the amount present at the point of attack, and to the removal of antiopsonins which may be present. Any therapeutic measure which will achieve these ends, without at the same time causing general dissemination of the localized infection or the admission into the blood-stream of excessive doses of toxins, is therefore to be recommended. The risk in all systemic infections is that by the injection of the vaccine into the body of a patient already staggering under so heavy a dose of toxin as he can possibly bear, such a further amount might be added as would just suffice to overtax his power of resistance. There is, however, this difference between the injection of a bacterial vaccine into the subcutaneous tissues and the introduction of bacterial poisons directly into the blood-stream, that in the former case the action is localized more or less to the site of injections, whereas in the latter there is a direct addition to the intoxication of the central nervous system and heart.

Considerations such as these have till recently prevented opsonic treatment being directed towards the cure of any systemic affection; but, as will be described later, there are certain such conditions when it may be

employed with the greatest advantage. It may, however, be conceded that the stricter the localization of an infection, and the less the machinery of immunization is being already called into play, the more favourable are the conditions for opsonic treatment. In pyrexial phthisis, as we have seen, such machinery is already being utilized, but the influx of bacterial elements into the blood is taking place from regions which are not in immediate relation to the blood-stream ; it is, moreover, discontinuous and due to causes which are more or less under control—viz., physical exercise and mental excitement. Wright instances two cases of phthisis which took part in a dance: their indices, never previously below 1, fell respectively to 0·12 and 0·33 ; also another case, whose index fell in connexion with overwork from over 1 to 0·2.

Before, then, commencing a course of administration of tuberculin in pyrexial cases, it is absolutely necessary to arrest the auto-inoculation by rest, physical and mental. A reduced and regular temperature and steady opsonic index, even at a much lower level, will indicate a return to a strictly localized infection, and the suitability of the case for a course of inoculation. While it is almost certainly true that the cessation of pyrexia indicates a localization of the tubercular infection, yet, since such cases are usually cases of mixed infections, it means more than this : that the pyrexia is entirely due to absorption of tubercular toxin is very unlikely, a dose of tuberculin (T.O.) that would produce such a reaction would result in changes of the opsonic index in no wise comparable with the short positive and negative phases that are found. It is in the absorption of the toxins of the secondary infection, and perhaps to the dissemination into the blood-stream of small doses of living bacteria, that the

true cause of the pyrexia more probably lies. Cessation of the high temperature may therefore be taken to indicate restricted outpouring of tubercular and other toxins, and localization of the primary and secondary infections alike. Failure to secure this fall of temperature would, on the contrary, indicate the reverse of this. The question thus arises as to what is to be done in these cases of continued pyrexia.

As experience increases it becomes more and more impossible to draw any hard-and-fast line between cases that are suitable for a course of tuberculin and those that are not, for cases have frequently done well which seemed quite hopeless.

For this reason routine injection of even such cases as these has been warmly advocated. The administration of very small doses indeed of tuberculin (0·0001 milligramme), controlled by frequent and careful determinations of the index, can do little harm, and the futility of continuing such treatment will soon be revealed in any given case ; but even then our resources are far from being exhausted. No one who is familiar with tubercular bone disease needs telling how well purely tubercular cases do, and how intractable are those of mixed infection. To attempt the treatment of cases complicated by secondary infection by means of tuberculin, leaving the secondary infection to cure itself, is undoubtedly bad procedure. A simultaneous attack upon the tubercle bacillus and the pyogenic cocci by means of a vaccine yields very much better results. Cases of advanced pulmonary phthisis are on an exact par with these mixed bone infections. The determination of the exact nature of the secondary infection by examination of the sputum is both difficult and unreliable ; examination of the con-

tents of an actual cavity is alone satisfactory. Attempts have been recently made to secure such material by means of trocar and cannula, and with a measure of success. Improvements in modern surgery have, moreover, brought the lungs within the zone of operation. Sir William MacEwen has recently successfully excised a portion of lung containing a phthisical cavity, and thereby demonstrated the possibility of attaining an unexpected measure of success in the opsonic treatment of such otherwise hopeless cases of phthisis.

Trudeau's Results.

From 1890 to 1901 Trudeau in America employed inoculation treatment in cases of pulmonary phthisis. The adjoined table is a comparison of the results obtained by pure sanatorial measures with those supplemented by inoculations of tuberculin.

TABLE X

(1) Cases treated (Non-Tuberculin).	(2) Cases treated with Tuberculin.	Advantage to (2) over (1).
1,367 Alive, 38·0 per cent. Dead, 36·6 „	143 Alive, 58·0 per cent. Dead, 33·0 „	20·0 per cent. 3·6 „
Balance untraced		

Incipient Cases only.

(1) Cases treated (Non-Tuberculin).	(2) Cases treated with Tuberculin.	Advantage to (2) over (1).
Alive, 61·0 per cent.	Alive, 76·7 per cent.	15·7 per cent.

Bearing in mind that the opsonic theory was unknown, and that, therefore, guide as to the right time for inoculation was quite lacking, the results can only be described as very striking.

In undertaking the opsonic treatment of any tubercular infection, the extreme value of the results of clinical experience must not be lost sight of, and to these due deference must be paid. For instance, a course of tuberculin having satisfactorily raised the opsonic index in a case of tubercular hip, theory might perhaps advocate an increase in the amount of lymph rich in bactericidal substances being brought to the part by means of movement and massage. Clinical experience has, however, shown the extreme inadvisability of such measures, and the wise will accordingly leave them alone. Surgery, then, and opsonic treatment are to go hand in hand. For tubercular glands in the neck, if not caseating, hygienic methods and tuberculin will probably suffice; if breaking down, the attention of the surgeon will be required, and the radical operation advocated by Watson Cheyne, removing all the fat as well as the glands, will receive assistance from a course of tuberculin.

A case of early joint disease should be met by splints, rest, and tuberculin. Should the disease be advanced and the surgeon decide on excision, then a preliminary raising of the index by means of tuberculin will minimize the risk of dissemination, and a continuation of such treatment after the operation will expedite the cure. It may, however, be noted that cases of this kind, so advanced that even amputation was advocated, have cleared up in such a marvellous manner under tuberculin and the usual therapeutic measures that no case need be considered hopeless until such measures have been given trial. (See Chart XI. for instance of such.)

Tubercular peritonitis, either with or without laparotomy, whereby fluid almost devoid of bactericidal power is replaced by fluid rich in opsonins, has also done well, while hope of success may even be held in tubercular meningitis.

In tubercular ulceration of the intestine, however, the results so far have not been altogether encouraging ; the employment in these cases of a tuberculin of bovine origin may give better results.

Tuberculosis of the Urinary System.

Pardoe[1] lays stress upon the frequency and non-recognition of this form of tuberculosis, and especially of that of the bladder. So disappointing have been the results of operative treatment and of all kinds of bladder washes and instillations that he declared that he himself had never met with a case even of apparent cure of vesical tuberculosis by such means. Tuberculin treatment has here met with success that can only be called brilliant. Pardoe himself treated twenty-one cases with tuberculin, many of these before opsonic work was known. Despite this fact, and the certainty, as he himself admits, of having at times given much too large doses and at improper intervals, he obtained the following results :

TABLE XI

	Per Cent.		Per Cent.
Cured 5 cases out of 21	24	No improvement in 6 cases out of 21 ..	28
Greatly improved 4 cases out of 21	19	Death in 6 cases out of 21	28
	43		56

[1] *Lancet*, December 16, 1905, p. 1766.

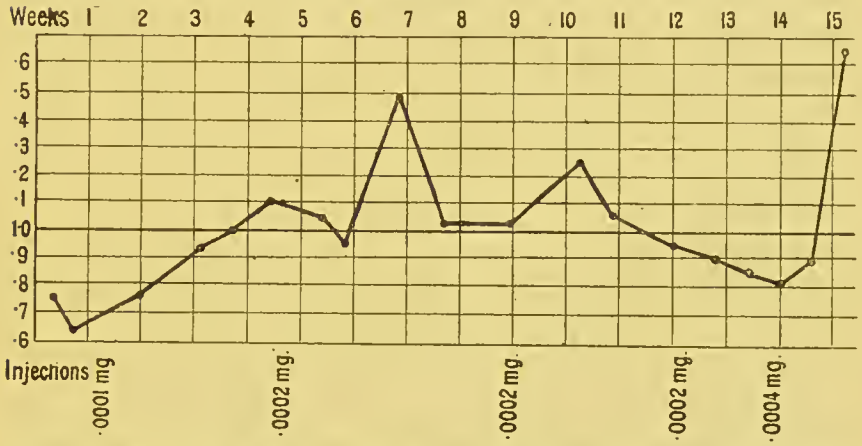
He, however, considers that tuberculin should never be given in genito-urinary cases if the orifices of both ureters are infected.

Other observers whose work has been guided by opsonic determinations do not agree with this, and have obtained even more encouraging results. (Chart No. XII. affords an especially good instance of this.)

Hurry Fenwick advocates the use of tuberculin to begin with, excision to be resorted to if the ulcers are seen not to be healing, by the aid of the cystoscope.

CHART XI (Dr. J. W. E.)

Severe Tuberculous Synovitis of Knee. First Four Months of Treatment.



Fluid from joint when inoculated into a guinea-pig produced typical generalized tuberculosis in eight weeks. Complete cure in six months, with perfect mobility of joint.

Tubercular Eye Disease.

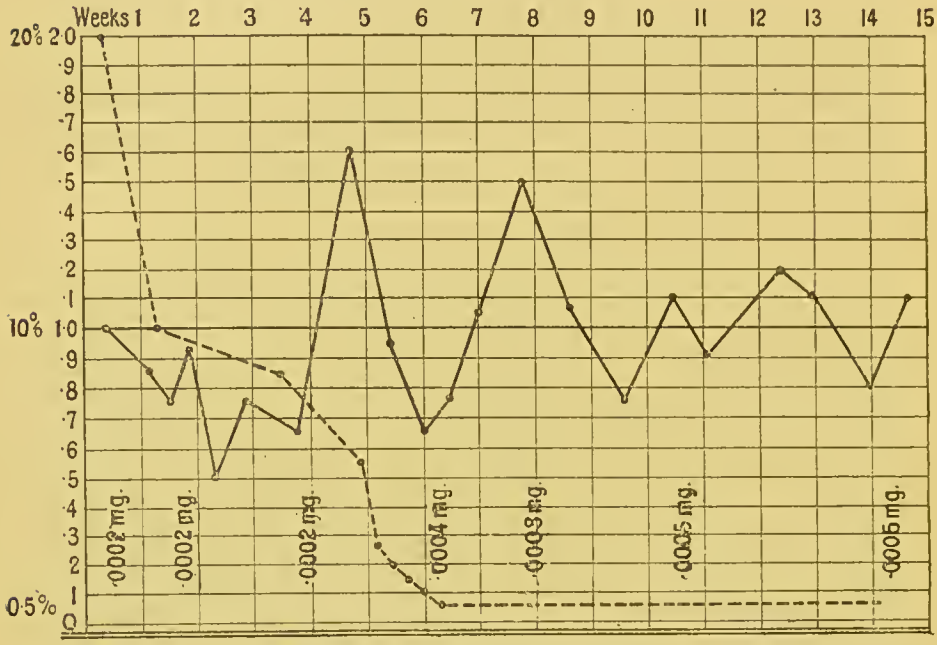
So successful has tuberculin proved in this class of case that Professor von Hippel holds that T.R., rightly used, will cure the severest tuberculosis of the eye.

Brown[1] records the complete cure of a case of tuber-

[1] *Journal of the American Medical Association*, October 14, 1905.

cular iritis after six months' treatment with T.R. The author himself has treated three such cases, as well as several of keratitis, with gratifying results.

CHART XII (Dr. J. W. E.)



Dotted line=percentage of pus in urine.
Continuous line=tuberculo-opsonic index.

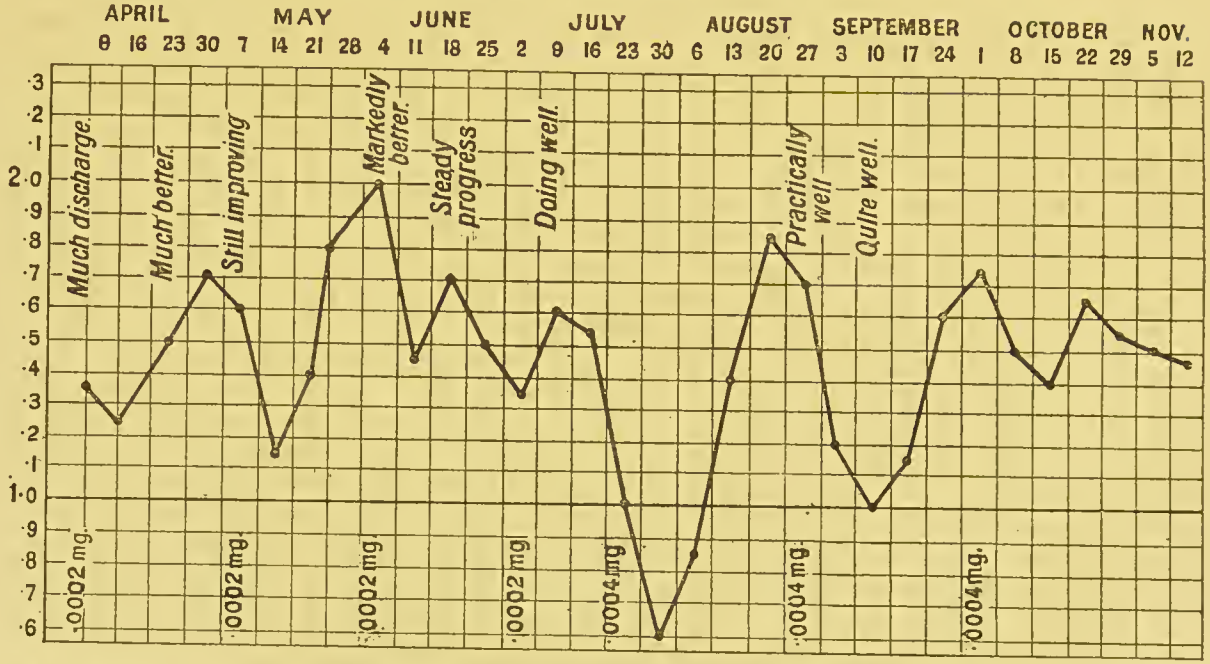
This chart exhibits the first four months' result of treatment in a very bad case of renal and vesical tuberculosis. The cystoscope showed advanced disease of the right kidney, slightly earlier in the left kidney, and advanced in the bladder. The patient improved greatly under treatment, and was alive and in fair health two years from the commencement of treatment.

Choice of Tuberculin.

In this connexion two important points are worthy of notice. In the first place, accidents have arisen with some preparations from the presence of living bacteria capable of multiplying. This risk has been obviated by the discovery of Wright that tuberculin may be heated

CHART XIII

CASE OF CARIES OF SUPERIOR MAXILLARY BONE. PURE TUBERCULAR INFECTION.



It will be noticed that the injections of 0·0004 milligramme on July 23 and August 27 produced very great fluctuations in the index, indicating that these doses were unnecessarily large. The patient, however, continued to do extremely well, and on September 10 no sign of the injection remained beyond a slight scar. The considerable reaction of index to injection, however, indicated that in all probability tubercle bacilli were still present. Injections of reduced doses were therefore continued until the index remained practically steady.

to 60° C. for one hour without suffering deterioration. This suffices to kill any living bacteria, while the addition of 0·2 per cent. of tricresol further minimizes any risk. The best preparation of T.R. is that of Meister Lucius and Brunnig of Hochst, which is put up in phials containing 10 milligrammes of solid substance per c.c.

The second point is perhaps a yet more important one, but unfortunately involves a discussion of the intestinal origin of tuberculosis and of the relative importance of the human and bovine types of the tubercle bacillus.

As is well known, Koch and Behring hold diametrically opposed views upon these points. Koch considers that human and bovine tuberculosis are separate and distinct diseases, and that bovine tuberculosis, if conveyed to man, cannot set up generalized tuberculosis, and that this disease is spread by direct infection.

Behring, on the contrary, maintains that the two are the same disease, and that nearly all tuberculosis is the result of infection during infancy by means of infected milk, and that direct infection from person to person is not proved.

Raw holds a middle view, and believes the two, human and bovine, are distinct varieties of an original species, yet sufficiently distinct to produce different and characteristic lesions in the human body; also that bovine bacilli give rise to a large amount of tuberculosis in children through infected milk. He considers that the glands in the neck are infected by absorption of bovine bacilli in milk through the tonsil and pharynx; that the lungs are generally infected by inhalation of bacilli from a previous case of phthisis, but that very occasionally the apex of the lungs is attacked by extension down the neck from tuberculous glands; that the lungs are frequently attacked, especially in children, by direct lymphatic extension from

the mesenteric glands through the diaphragm to the pleuræ and lungs, there setting up acute miliary tuberculosis, which he thus hold to be bovine, and not human, in type. In support of these views, he adduces the fact that out of 4,000 cases of pulmonary phthisis which he had seen, and over 1,600 autopsies which he had made, he had only found the cervical glands or joints affected in fifteen cases ; but, as West has pointed out, phthisis is very rare without an antecedent tuberculous focus, usually in the mesenteric or mediastinal glands, although this may have quite healed. McConkey and MacFadyen have found virulent tubercle bacilli present, usually in the mesenteric glands, of about 25 per cent. of children who have died from non-tuberculous causes.

Raw's contention that miliary tuberculosis, primary intestinal tuberculosis, tuberculous infection generally of the serous membranes in children, together with lupus, tubercular glands and joints, are due to infection by the *typus bovinus*, whereas that pulmonary phthisis, excluding the miliary form, is due to infection by the *typus humanus* receives support from the following observations. The German Government Commission, in examining fifty-six cases of human tuberculosis, found the *typus humanus* in fifty cases, in the other six the *typus bovinus*. These last were all in children under seven years of age, and the nature of the cases was as follows :

1. Tuberculosis of mesenteric glands.
2. Ditto.
3. Ditto, with intestinal tuberculosis.
4. Ditto, with tubercles in spleen and pleuræ.
5. General miliary tuberculosis of lungs and meninges.
6. Acute general miliary tuberculosis, involving practically all the organs.

In Siam, where cow's milk is never drunk, pulmonary phthisis is rampant, but tuberculous glands and joints and lupus are unknown. A similar condition is found in Egypt, Malaya, India, and Persia.

Dungerm and Smidt,[1] experimenting on gibbons in Sumatra, found that animals infected by feeding with bovine bacilli exhibited tubercular ulcers of the small intestine and caseous mesenteric glands ; whereas when human bacilli were employed no lesions were to be found in the intestine or mesenteric glands. It would therefore appear as certain that man does become infected by both the human and bovine type indifferently. The bearing of this upon the source and nature of the tuberculin used is obvious. The lesson learnt from opsonic work upon all other organisms is the necessity, wherever possible, of preparing the vaccine from the patient's own strain ; failing this, a freshly isolated active young strain, corresponding as closely as possible to that of the patient, must be employed. Yet here for years past bovine and mixed bovine and human infections, as well as purely human ones, have been treated with tuberculin prepared from the human type. Small wonder is it that failure has attended a certain proportion of efforts.

Raw in this connexion takes up the attitude—extraordinary in view of the fact that it demands the premise that tubercular infections therein differ from those due to all other organisms—that infections due to the bovine type do best with tuberculin of human origin, and presumably, *per contra*, that those due to the human type will do best with tuberculin of bovine origin. His reasons for this view appear of little weight, and are based upon

[1] *Arbeiten aus dem Kaeserlichen Gesundheisamte*, Bd. xxiii., H. 2, 1906.

the observations that phthisis rarely develops in cases of tubercular glands or joints, and then it is of the miliary type; that lupus and phthisis rarely occur together; and that, as Romburg and Behring have shown, the only way to secure complete immunity in cattle against tuberculosis is by inoculations with the human type.

This he considers demonstration that the two varieties of tubercle bacilli are antagonistic to each other, and that a mild bovine infection in early life confers a certain immunity against phthisis, just as vaccination does against small-pox. In view of the fact that old tubercular infection, presumably of bovine origin, is nearly always discoverable in the mesenteric or mediastinal glands in cases that die of pulmonary tuberculosis, this idea of a protective action of bovine infection is based upon considerations of little value.

Without attempting to explain the fact that the human strain does undoubtedly the more strongly immunize cattle against the bovine strain, I would urge the view as more rational that, despite the employment of a more or less ill-adapted tuberculin, good results have been obtained in tubercular infections, both of the human and bovine strain, and that the use of an appropriate tuberculin would yield still better results than any yet obtained.

The author, as well as other observers, is at present conducting a series of cases upon these lines, but too few observations have been made to enable any definite conclusions to be formed. Meantime, it is perhaps as well to begin the treatment of any case with ordinary T.R.; but if no improvement results in three or four injections, continuation with T.R. of bovine strain is worth consideration.

The Conduct of a Case undergoing Tuberculin Treatment.

A course of tuberculin treatment having been decided upon, the first thing to be done is to put the patient under the best hygienic conditions, secure abundance of fresh air and good food, and by rest in bed reduce a case of pyrexial to an apyrexial condition whenever possible.

In cases of acute pulmonary phthisis it is especially necessary to make from day to day a series of estimations of the opsonic index, until such time as it remains steady and indicates localization of the injection. The first dose of tuberculin should be a minimal one ($\frac{1}{10000}$ to $\frac{1}{5000}$ milligramme). The patient should be kept in bed to ensure the prevention of fresh auto-inoculations, and the index taken daily until the negative phase has passed off and the crest of the positive phase attained. Only in this way can the correct dosage be estimated. Should no adequate response be obtained, the dose is gradually increased until one is. This dosage is then adhered to for two or three injections, and only gradually and carefully increased, being controlled by estimations of the index taken every seventh, or, better, every third, day. In this way a maximum dose of 0·01 milligramme may finally be attained. The difficulty in obtaining a cumulative positive phase in phthisical cases is indeed great, but not altogether impossible. To this end too long an interval must not be allowed to pass after the crest of the positive phase has been reached. The lapse of two or three days will usually suffice, for injection when the index is falling at all rapidly results in a pronounced depression. Rather than allow this to happen, inject even before the full rise has

oeeurred. Completion of the eourse of treatmcnt is indieated when the by now largely increased doscs fail to eause any marked disturbance of the raised index. This point eannot, however, be always obtained, even in eases in whieh subsequent events justify thc view of a eure having been obtained. The dose should then bc diminished and the intervals increased, and the patient gradually brought baek to a state of aetivity.

Early eases of pulmonary phthisis, of lupus, and tubereular glands may, of eourse, be allowed regular exercise throughout the treatment, provided that no evidence of auto-inoeulation is afforded by irregular fluctuations in the index; rest in bed on the day of injeetion and that following is not even necessary. Only in cases of pulmonary phthisis is frequent determination of the index obligatory, in other eases too frequent determinations ean hardly be done until the appropriate dosage has been found : that attained, estimations on the eighth and seventeenth days subsequent to an injection will suffiee, for in 80 per cent. of cases the negative phase is over by the eighth day.

In the present state of knowledge the index remains the only safe guide; pulse, temperature, and even elinieal appearanee afford no indication of the proper time for injeetion.

To seeure the best results by tubereulin treatment, the following few golden rules must be followed :

1. Never inject without having first made a series (two or three) of estimations, to ensure the absenee of auto-inoeulations, and so minimize the risk of injeetion during a negative phase.

2. Estimate the index frequently after the first injection, in order to ascertain the amplitude and duration of

the negative phase, the positive response, and so the proper dosage.

3. Never subsequently inject 'blind'—*i.e.*, without doing the index the day before. Many mistakes will be obviated by following this rule.

4. Increase the dose slowly, yet sufficiently to secure each time a proper reaction.

5. Do not become discouraged; many cases seem to improve only after four or five doses. If improvement ceases even with greatly increased doses, try change of air, give one or two smaller doses, then stop for a month or two, and begin again.

6. When cure has been apparently effected, continue for a few doses more, reducing the dose each time and prolonging the interval.

The Indices of 'Cured' Sanatorium Cases and the Question of their Injection.

Lawson and Stewart[1] examined twenty-five cases of pulmonary phthisis 'cures.' In five of these the index was between 1·1 and 0·9; in the other twenty it was 0·8 or under. Twenty-three of these elected to be injected, with the results shown in Table XII.

The additional rise in antibacterial substances obtained by the inoculations subsequent to a long course of climatic and sanatorium treatment is very striking. Whether such cases with abnormally low indices are especially liable to relapse we know not, but Lawson is strongly of the opinion that no case of apparently cured phthisis with a low index should be discharged from the sanatorium until the index has been raised.

[1] *Lancet*, December 9, 1905, p. 1683.

The weight of accumulated evidence seems to point towards the view that the usual duration of sanatorium treatment is insufficient to produce permanent cure in any but the most incipient cases of pulmonary phthisis, and that tuberculin is a very powerful adjuvant indeed to the ordinary methods of such treatment.

TABLE XII

Case.	Index before Injection.	Index after Course of Injections.	Number of Injections.
1	1·0	1·1	1
2	0·9	1·4	3
3	0·9	1·4	3
4	0·9	1·2	3
5	0·8	1·4	3
6	0·8	1·0	4
7	0·8	1·3	5
8	0·8	1·1	1
9	0·8	1·0	3
10	0·8	1·2	2
11	0·7	1·1	4
12	0·7	1·5	3
13	0·7	1·0	2
14	0·7	1·3	3
15	0·7	1·3	4
16	0·7	1·2	3
17	0·7	1·3	3
18	0·7	1·3	4
19	0·7	1·3	4
20	0·5	1·1	5
21	0·5	0·8	2
22	0·5	1·5	4
23	0·5	1·1	5

CHAPTER VI

STAPHYLOCOCCAL, STREPTOCOCCAL AND PNEUMOCOCCAL INFECTIONS

The *Staphylococcus albus* and *aureus* may be the cause of inflammatory and suppurative processes all over the body. Among acute forms of infection may be instanced Suppurative Periostitis and Osteomyelitis, Ulcerative Endocarditis, Pleurisy, Peritonitis and Meningitis, Carbuncle and Furuncle, Endometritis, and various Pyæmic conditions; among its chronic manifestations are Acne, Ulcers, and Sycosis. It may also secondarily infect cases due to tubercle, *Bacillus coli communis*, *Bacillus typhosus*, and streptococcus, etc. Its relationship to chronic gleet is discussed under the chapter on the Gonococcus. Opsonic treatment in this connexion finds great scope in such localized infections as Acne, Sycosis, Furuncle, Ulcers, and secondary bone infections.

The index in these cases is consistently subnormal, varying from 0·2 to 0·8. The isolation of the organism in such cases has already been dealt with, and also the method of preparation of the vaccine. This organism is an especially easy one to deal with in every respect. The response to injection is always marked by such definite clinical reactions that frequent estimations of the index may, as a rule, be dispensed with. Indeed, some venture after the first two or three injections to do without them altogether. The negative phase is nearly always indi-

cated by a crop of suppurative foci, which, however, abort in a day or two. The appearance of a second crop is the signal for a fresh injection, which is usually required at intervals of fourteen to twenty-one days. Personally, however, I think it better practice always to do the index the day before a proposed injection. A very suitable dose to commence with is 250,000,000 organisms ; this soon requires increasing to 500,000,000 and 750,000,000, the necessity for this being evidenced by the recurrence of mild attacks. Later larger doses still may be necessary. In the worst case of acne I have ever seen doses of 1,750,000,000 bacteria were given towards the end of treatment at fortnightly intervals, the index then remaining steadily between 0·9 and 1·2 (see Chart XIV.). Treatment must be persisted in even for six or eight months, until not only do fresh foci fail to appear, but even the old scars have begun to disappear. Diminished doses at prolonged intervals will in most cases complete the cure. In pyæmic cases large doses up to 1,000,000,000 cocci may be safely employed, and may have to be repeated at very short intervals as the index falls and rises.

A small percentage of cases either remain obdurate or else relapse after a partial cure. It is then better to desist for a few weeks, prepare a fresh vaccine, and begin again, or else resort to other means of raising the index, such as yeast by the mouth or nuclein subcutaneously. When staphylococci complicate a tubercular infection, as in psoas abscess, joint and bone disease, opsonic injections will prove of the utmost assistance to the surgeon ; indeed, I have seen several cases which persistently refused to get well clear up as if by magic after two or three injections of staphylococcal vaccine as adjuvant to tuberculin.

CHART XIV

VERY SEVERE ACNE OF FACE, NECK, SHOULDERS, AND BACK.

Streptococci, like staphylococci, cause inflammation and suppuration in all parts of the body. Till quite recently reliance was placed upon injections of antistreptococcic serum in such conditions as Erysipelas, Pyæmia, Puerperal Fever, Periostitis, and Endocarditis. The large proportion of cases in which failure was recorded, and the recognition of the fact that the streptococcus is a large genus and not a single individual, has induced greater attention to be paid to the preparation of a vaccine from the patient's own organism and its administration, safeguarded by estimations of the opsonic index. Experience in this direction, though very limited, has yet proved decidedly encouraging. Most successful results have been gained in the treatment of such diverse infections as Erysipelas, Empyema (55 per cent. of which in adults and 15 per cent. in children Netter has shown to be due to the streptococcus), secondary joint infections, Dacryocystitis, and even infective Endocarditis, while possibilities would seem to exist for its employment in cases of Acute Articular Rheumatism. The utility of vaccine therapy in Infective Endocarditis and Pyæmia is so striking, in that it is an instance of successful treatment of acute systemic infection, that a short account may be given of two cases.

The first case was described by Sir James Barr before the Liverpool Medical Institute on May 3, 1906, the treatment having been conducted by Captain Douglas. It was a very severe case, rigors occurring every twenty-four hours or oftener, when the temperature mounted to 104° or 105° F., and was followed by profuse sweating. There was an attack of pleurisy with pleuro-pericardial friction, but without marked effusion. All the various brands of antistreptococcal serum had been tried, without much benefit.

Douglas isolated the streptococcus from the patient's blood, and a vaccine was made. The index was estimated twice daily, and injections given of 10,000,000 cocci at each fall of the index.

The patient made an excellent recovery, and, except for the effects of phlebitis in the left lower limb, was soon quite well.

Sutcliffe and Baily[1] have described a case of streptococcal septicæmia in a boy of fourteen, who had been operated on for discharging tubercular glands, which was successfully treated with a streptococcal vaccine. Pus was found along the track of the right deep femoral vein, and there was threatened formation in a similar situation in the left thigh. The cocci were isolated from the blood, and the index found to be 0·66. An injection of 10,000,000 organisms raised the index to 1·15 by the following day. In the course of forty-five days ten injections, varying in amount between 10,000,000 and 50,000,000 organisms, were given. Reduction of temperature, elevation of the index, and general improvement in the patient's condition ensued after each injection, and complete recovery was the ultimate result. Upon two occasions when manipulation of the limb was performed considerable depression of the index, due to auto-inoculation, was observed the next day.

The index in streptococcal infections may show great fluctuations, and may rise to great heights, indices even as high as 10 having been reported. The dosage also of the vaccine is unusually low; no more than 50,000,000 should be given as an initial dose, and doses of 250,000,000 organisms should rarely be exceeded. In septicæmic cases a first dose of 10,000,000 organisms would appear to suffice, but frequent repetition may be necessary.

[1] *Lancet*, August 10, 1907, p. 367.

The view has steadily grown in favour of late that streptococci are intimately connected, at all events, with the complications of scarlet fever, if not with the pathogenesis of the fever itself. Thus, in over 70 per cent. of cases with albuminuria streptococci are copiously voided in the urine, and in about 15 per cent. of cases without albuminuria. Bearing this in mind, Banks[1] has studied the variations in the opsonic index of the blood to streptococci as the disease progressed. He found that in cases running a fairly normal course the opsonic power towards streptococci varies in a pretty definite and constant way. It is decreased during the early febrile period, and rises to normal or above normal during the defervescence and general decline of symptoms. It falls during the second and third weeks, and even in uncomplicated cases the index may be comparatively low. There is an increase to normal or over during the fourth and fifth weeks. In fatal cases with severe angina the opsonic power is markedly subnormal. Complications alter the usual curve, causing both absolute and relative differences. Thus, the opsonic power is decreased at the onset and during the earlier period of albuminuria and secondary adenitis ; as convalescence is established the index rises. The opsonic values do not furnish many data for prognosis, but, in general, a persistent low index during nephritis or other serious complication is an unfavourable sign.

These results closely resemble those obtained by Macdonald (*vide infra*) in cases of pneumonia, both with and without complications. Bearing in mind the fact that the angina, adenitis, and nephritis of scarlet fever are due to localized streptococcal infections, the advisa-

[1] *Journal of Pathology and Bacteriology*, October, 1907, p. 113.

bility of artificially raising the opsonic index by means of a bacterial vaccine in cases so complicated appears to be worthy of consideration.

The Pneumococcus

causes a great variety of suppurative conditions, among which are Pneumonia, Pleurisy, Pericarditis, Endocarditis, Peritonitis, Empyema—both pulmonary (according to Netter, 15 per cent. of adult secondary cases and 65 to 90 per cent. of all cases in children) and of the accessory air sinuses—Otitis, Meningitis, Conjunctivitis, Arthritis, Periostitis, Nephritis and Perinephritis, Metritis and Pyosalpinx, Abscesses, and Pyæmia. It is also the cause of chronic Ulcus Serpens Corneæ.

The Index in Pneumonia.

MacDonald[1] studied the index in eight cases of pneumonia, and found that while the temperature is rising and during the fastigium the opsonic index is below normal, whereas at the onset of the crisis there is a sudden rise, even as high as 1·6.

Subsequent observations have shown that in very severe cases failure of the index to rise in this manner at the crisis is a matter of very grave importance, and that such cases usually die.

Recent attempts have been made in America to treat pneumonia as a routine by injection of a vaccine, and considerable success has been claimed. The temperature is said to fall several degrees within twenty-four hours; the crisis is precipitated within three or four days, and the

[1] Pathological Society, London, January 17, 1905.

convalescence is rapid and complete. The whole duration of cases so treated is claimed to lie within a fortnight.

Coleman recorded before the Royal Academy of Medicine, Ireland, on March 2, 1906, a case of unresolved pneumonia treated by inoculation of pneumococcal vaccine with very satisfactory results.

On the thirty-eighth day of attack the pneumococcic index was 0·6; 46,500,000 cocci were therefore given. There was no disturbance, local or general. Next day the index was 0·69, and the physical signs were those of pneumonia of five or six days' standing.

6 days after injection the index .. = 1·17 and the patient was much better.
10 ,, ,, ,, ,, = 0·89 and 46,500,000 were again given
3 days after second injection the index = 1·13.

Eleven days after the second injection the patient was in excellent health, and for six weeks subsequently the index was observed to be slightly over normal.

Wright, in a case of pneumococcal infection of the salivary glands with profuse salivation, failed to achieve cure, but produced distinct amelioration.

Cases of Empyemata where free drainage can be maintained, of Metritis and Pyosalpinx, of Periostitis and Osteomyelitis, are very favourable for opsonic treatment. Initial doses of 100,000,000 cocci are perhaps best, and great rise in the index, to 3 or even 5, may be anticipated.

The author has treated two cases of Ulcus Serpens Corneæ with complete success by means of vaccines prepared from the patients' own organisms. One of the cases deserves further mention. The patient was a man of eighty years of age, under the care of Mr. Brookbanks James, and was admitted with a very bad corneal ulcer.

A large hypopyon was present; the cornea was very opaque, the iris bound down by adhesions, and the tension +1·5. Cauterization, paracentesis, and, later, sclerotomy for the relief of tension and evacuation of the hypopyon, brought only temporary improvement, and excision seemed the only remedy. The condition was still acute when the pneumococcus was isolated and a vaccine prepared. Despite the high index to this organism—viz., 2·5—an injection of 250,000,000 organisms was given. Within three days the eye began to improve in appearance; at the end of a week the index was 4·2, and after a fortnight 3·0. A second injection was then given, with the result that eighteen days later the index stood at 6·3 and the inflammation had quite subsided. A large partial staphyloma of the cornea which developed later was treated radically by excision without the use of sutures. No reaction followed the operation, and the final result was an eye in which some slight vision was preserved, and a firm flat scar in the cornea left in the site of the staphyloma. Several months later the eye was quite quiet and free from irritability.

CHAPTER VII

THE GONOCOCCUS

The chief conditions set up by this organism are Urethritis, Periurethritis, Prostatitis, Vesiculitis, Cystitis, Epididymitis and Orchitis, Endometritis, Salpingitis, Peritonitis, Conjunctivitis, Endocarditis, Arthritis, and even Pleurisy and Septicæmia. In these connexions a very wide field of utility is afforded, both in the diagnosis and treatment.

The Opsonic Index in Gonococcal Infections, and its Utility in Diagnosis and Treatment.

In acute gonorrhœal infections of the urethra the index, as a rule, first falls for a few days to 0·6 or 0·7 ; it may then either rise steadily to 1·3 or 1·6, such cases usually doing well under routine treatment, or it may continue subnormal, when they usually pass on into a chronic intractable gleet.

In chronic cases the index is usually low, even 0·3 ; it is, however, sometimes normal or above normal, but in these cases cocci, as a rule, are to be found copiously in the secretions from suppurating Littré glands or sinuses, which may continue thus to discharge at intervals for many years.

In acute gonorrhœal conjunctivitis in adults the index may be as high as 2, or even 2·5.

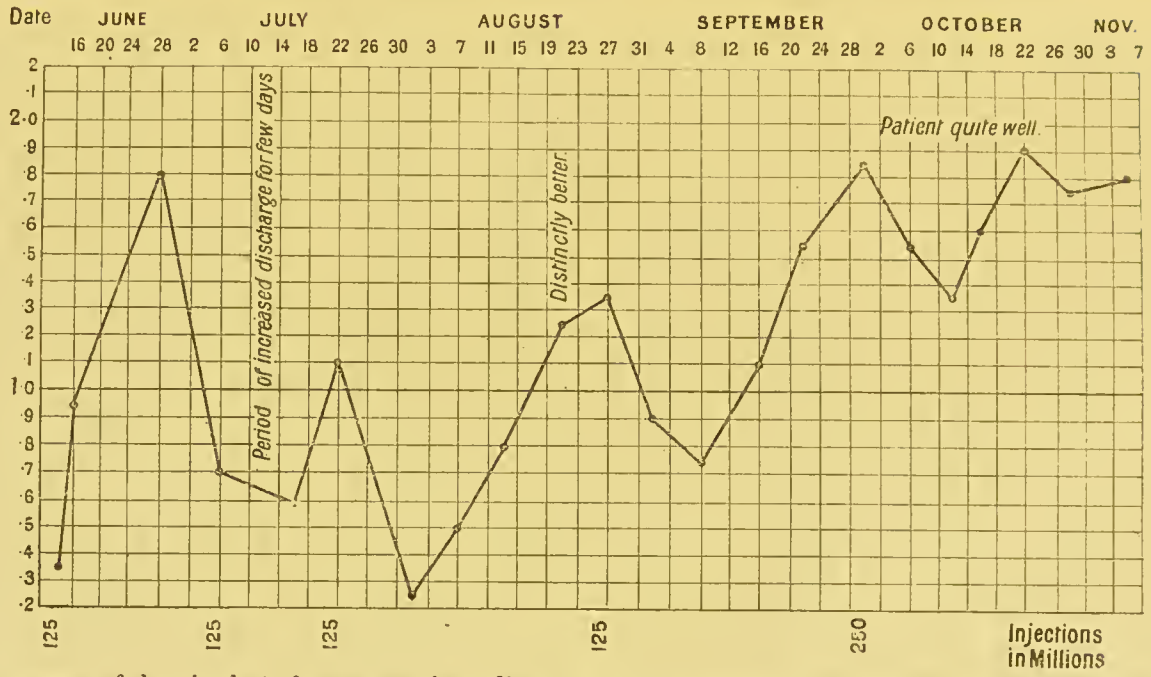
Every genito-urinary surgeon and obstetrician is familiar with the great difficulty of deciding whether an old gonorrhœal infection has disappeared, or of arriving at a diagnosis in cases where a history of an acute attack is not obtainable. In the male it is no very uncommon thing for a discharge to persist even for ten years after an attack of acute gonorrhœa. Stained films do not reveal the presence of any gonococci, but only of streptococci, staphylococci, the bacillus of Friedlander, the *Micrococcus catarrhalis*, and other + and − Gram organisms. The difficulty of advising as to the safety or otherwise of marriage in these cases is considerable. In deciding whether there are any latent gonococci encapsuled in the numerous urethral crypts and diverticula I have found the opsonic index of the utmost assistance. Brief reference to a few cases will illustrate this.

Case 1 had a chronic discharge for ten years. No gonococci could be found in films, but the bacillus of Friedlander was present in vast numbers in a state of purity.

The gonococcal index was 1·1, that towards the bacillus of Friedlander 0·6. Non-gonococcal infection was diagnosed, and treatment by means of a vaccine prepared from the pneumobacillus carried out with complete success.

Case 2 was one of twelve years' standing, which had proved obdurate to every form of treatment. No gonococci could be detected in smears or cultures, and the index was 1·2. The patient desired a course of injections with gonococcal vaccine, and five were accordingly given, but, as anticipated, without influencing the discharge. A combined vaccine was then prepared from the urethral

CHART XV.—Case of Chronic Gleet, exhibiting Prolonged Negative Phases.



This case was one of chronic gleet of seven years' standing. Slight exacerbations were frequent. The chart presents several points of interest. The Gonococcic index was very low—0·35—indicating exhaustion of the protective mechanism. Despite this, splendid response was made to the first injection, the index rising in fourteen days to 1·8, to fall as rapidly to 0·7. The second injection, of like amount to the first, produced a much less satisfactory result, the index being yet lower after ten days; upon the sixteenth day it had recovered to 1·1. A third injection was then given. Upon the tenth day the index had fallen to 0·25, but during this interval the clinical symptoms had altered little. The index then began to rise rapidly, and continued to do so for twenty-six days; as the limit of rise seemed about reached, a fourth injection was then given of 150,000,000 organisms. Study of the curve between the third and fourth injections shows clearly that the third was given prematurely. The rise after the first injection and the subsequent fall were both so rapid that I wished to avoid a similar fall after the second injection; hence the mistake, which was avoided subsequently.

organisms present ; two injections sufficed to reduce these greatly in numbers and variety, and a fresh vaccine was then made.

Two injections with this resulted in great diminution of the discharge, which contained only epithelial and lymphoid cells and few organisms, which were contained within the epithelial cells, and proved very difficult to cultivate. Subsequent irrigation for a few days with weak solutions of perchloride of mercury completely cured the discharge.

In these two cases, then, the gonococcal index was normal, and the diagnosis of non-gonococcal infection was amply confirmed by the results of treatment.

Cases 3 and 4 were each of ten years' standing, and had undergone the most expert surgical treatment, both in England and upon the Continent, but without avail ; exacerbations appeared from time to time without any obvious cause. In Case 3 no gonococci were to be found, in Case 4 only at intervals. The indices were found to be 0·4 and 0·5 respectively ; gonococcal infection was therefore diagnosed, and opsonic treatment advised, with complete success, two injections sufficing in the instance of Case 4.

Case 5 was sent me by Mr. Wyndham Powell, and is peculiarly interesting. The infection, which was a first one, dated back about three months, and had been diagnosed as a simple non-gonococcal urethritis by an eminent Parisian surgeon. Mr. Powell was of the same opinion, but, owing to the extensive involvement of Littré's glands, desired confirmation. Cultures of the secretion gave pure *Staphylococcus albus*, even after thorough irrigation of the urethra. The gonococcal index was found to be 0·9. The staphylococcal index was found to be 0·7.

Confirmation was thus afforded of the non-gonococcal nature of the infection, which was considered to be staphylococcal in nature. A vaccine was made, and an injection of 150,000,000 organisms given. A second similar injection was given three weeks later, and the patient appeared to be improving. Unfortunately, he left England a fortnight later, and the success or otherwise of the treatment could not be determined.

Case 6 was a case of old gonococcal infection in the female, the discharge recurring at practically every menstrual period. Advantage was taken of the fact that during a period the index towards any infecting organism falls considerably : two days prior to menstruation the index was found to be 0·7 ; upon the fourth day is was only 0·3. The diagnosis of gonococcal infection was therefore made, and amply confirmed by the results of opsonic treatment. In three months the woman felt a totally different person, and had gained a stone in weight.

The evidence afforded by these and numerous other cases of chronic urethritis serves to indicate that in many instances, though the gonococcal infection has died out, the gonococcal toxins and antiseptics faultily applied have resulted in a weakened mucous surface, upon which numerous pathogenic organisms, usually of low virulence, are enabled to flourish and multiply. These prove extremely resistant in many instances to local forms of treatment, but readily respond to injections of vaccines, a series of which may, however, be required. In view of the extreme importance of eliminating every chance of the continuance of a gonococcal infection, it is good practice in all cases where the index is on the border-line of the normal—*i.e.*, 0·8 or 1·2—to begin the treatment of such cases with injections of a gonococcal vaccine, even

though no gonococci are to be found in the secretion. A first dose of 75,000,000 organisms is best given ; should this produce no effect, it may be followed by a second of double the amount. Should only slight disturbance of the index result, the non-gonococcal nature of the infection may be considered established, and treatment then begun with a combined vaccine. Such treatment can do no possible harm, and may prevent a gonococcal case being missed. It must, however, be noted that even persistent treatment of some cases of chronic urethritis will fail to entirely cure the discharge and threads in the urine. The patients feel better, suffer no discomfort, and put on weight, yet a small bead of discharge may be expressed in the morning. Such cases may safely be left in such a condition, none having retrogressed within my experience.

I have of late made a routine practice of giving every case of acute gonorrhœa one or two injections of vaccine, the first being administered as soon as the acuter symptoms have begun to subside and the thick discharge to diminish. Convalescence has been complete in two or three weeks, and secondary complications and backward extension have failed to appear in any of the series. This procedure can be warmly recommended.

Acute gonococcal conjunctivitis in the adult is a condition of extreme gravity ; unless taken in hand early, the chances of destruction of the sight are very considerable. Such a case under Professor McHardy was seen by three members of the staff at the Royal Eye Hospital, and so bad a prognosis given that immediate injection with a gonococcal vaccine was decided upon. The large dose of 250,000,000 organisms was administered, and the index found to be 2·5. Although the patient was extremely negligent of himself, and could not be induced

to use a lotion regularly, improvement began immediately, and, despite the fact that on the fourth day the negative phase was still persisting, the index being only 1·26, marked change was evident : the active process was checked ; there was much less chemosis and little discharge. Upon the eighth day the index was 3·8, and the condition of the eye so satisfactory that the patient could not be induced to make any further attendance.

The treatment of gonococcal arthritis has also proved very satisfactory, while success has also been achieved in cases of septicæmia.

Despite the researches of Torrey,[1] who, from a study of the agglutinins and precipitins in antigonococcal sera, came to the conclusion that the family gonococcus is heterogeneous rather than homogeneous, the view of its being a definite entity is usually held. Wherever possible, it is undoubtedly best to prepare a vaccine from the patient's own organisms ; but should the virulence of these have been reduced by antiseptic treatment or by the long duration of the infection, it is decidedly better to employ a vaccine made from a strain of known high virulence. In eye cases one should inject immediately the diagnosis is established, without waiting to determine the index or prepare a vaccine. The index in all eye infections, acute or chronic, due to whatever organism, is, as a rule, exceptionally high. The reason for this is fairly obvious. The circulation of that part is poor, the area of infection small ; consequently the toxins formed are absorbed in such minute quantities that they act like very small doses of vaccine. and tend to raise the index. If other areas in the body are infected, as is often the case in tubercular cases, this reasoning does not apply,

[1] *Journal of Medical Research*, Boston, May, 1907, p. 329.

and the index corresponds to the nature of the other area of infection. That the already high index so often fails to effect cure in these cases is due to the same cause—poor blood-supply and poor lymph flow ; hence in such cases high index is no contra-indication to injection.

The dosage in gonococcal cases requires particular attention. Owing possibly to the powerful toxins formed by this organism, the initial doses employed are smaller than in the case of most other organisms : 50,000,000 organisms may be used with advantage upon the first occasion, 100,000,000 being employed upon the second, if indicated by the index. Subsequently larger doses than 250,000,000 are not often required.

As regards the frequency of administration, this should always be controlled by determinations of the index. A negative phase, lasting for a fortnight, with a dose of 100,000,000 or 150,000,000 organisms, is by no means infrequent, in which case little advantage can accrue from fresh injection before the end of a month.

As in the case of tubercle, it is particularly bad practice to inject without estimating the index the day before ; if this cannot be done, it is better to err on the side of waiting a week too long rather than on that of injecting a week too soon. It may, however, be noted that occasionally the result of a first injection is a continued negative phase ; the index drops a few decimal points, and is only raised by a second injection of like strength. Should, however, the index still remain depressed, it is best to wait four or five weeks, and begin again with reduced dosage.

Another peculiarity about this organism is the marked improvement of clinical features which occasionally

results during the negative phase. Increased discharge often occurs during the first two or three days, but then rapidly diminishes, despite the continued presence of the negative phase. Clinical symptoms are therefore a totally unreliable guide as to the appropriate time for fresh injections.

CHAPTER VIII

THE OPSONIC TREATMENT OF CATARRH, NASAL AND TRACHEAL, AND OF THE ACCESSORY AIR SINUSES

During the last three years the author has been working continuously upon this question. A paper will shortly appear, but some of its essential features may here be given.

The Bacteriology.

1. *Of Nasal Catarrh.*—Thirty cases of nasal catarrh, acute and chronic, were examined bacteriologically and the causative organisms determined, with the following results:

The bacillus of Friedlander alone in 8 cases ..	= 27·0 per cent.
The *Bacillus influenzæ* alone in 1 case ..	= 3·3 ,,
The *Bacillus septus* alone in 8 cases ..	= 27·0 ,,
The *Micrococcus catarrhalis* alone in 6 cases	= 20·0 ,,
The bacillus of Friedlander + *Bacillus septus* in 3 cases	= 10·0 ,,
The bacillus of Friedlander + *Micrococcus catarrhalis* in 1 case	= 3·3 ,,
The *Bacillus septus* + *Micrococcus catarrhalis* in 3 cases	= 10·0 ,,

Considering the acute and chronic forms separately, the following causal relationship was determined:

	Bacillus of Friedlander.	*Bacillus influenzæ.*	*Bacillus septus.*	*Micrococcus catarrhalis.*
Acute ..	Yes	Yes	Yes	Yes
Subacute ..	Yes	Rarely	Rarely	Yes
Chronic ..	Yes	No	No	No

It would thus appear that the only common cause of non-suppurative chronic nasal catarrh is the bacillus of Friedlander.

2. *Of Tracheal Catarrh.*—The *Bacillus septus* would appear never to set up this condition ; the bacillus of Friedlander very exceptionally ; the *Bacillus influenzæ* and the *Micrococcus catarrhalis* habitually.

It must, however, be noted that the latter of these is frequently present in perfectly healthy tracheas, just as in certain healthy individuals the pneumococcus is always to be found in their sputum. A catarrh of the trachea set up by the *Micrococcus catarrhalis* soon, moreover, becomes secondarily infected with other organisms, just as does a catarrh of the conjunctival or urethral mucous membranes. The prime factor is, however, the *Micrococcus catarrhalis*, which is also, I believe, the probable cause of many cases of bronchitis.

3. *Of the Accessory Air Sinuses.*—Lewis and Logan Turner[1] made a number of careful bacteriological examinations, both in the cadaver and on the living subject. A great variety of organisms were found, chief among which were the staphylococcus, streptococcus, pneumococcus, and bacillus of Friedlander. Just as in the case of the lachrymal duct the acute infection due to Koch-Weeks bacillus, the *Bacillus lacunatus*, *Bacillus coli*, staphylococcus, or gonococcus becomes secondarily infected by the *Streptococcus pyogenes*, which ultimately displaces the other organisms altogether, and maintains a chronic dacryocystitis, so I believe in these cases the prime infection in many cases to be due to an attack of acute nasal catarrh due to the *Bacillus influenzæ*, bacillus of Friedlander, *Bacillus septus*, or *Micrococcus catarrhalis*,

[1] *Edinburgh Medical Journal*, November, 1905.

and that the staphylococci, streptococci, and pneumococci are secondary infections, maintaining a chronic condition. This probably affords ample explanation of the fact that chronic nasal catarrhs with sinusitis fail to give entirely satisfactory results, as we shall see, with vaccine of the bacillus of Friedlander.

The Opsonic Treatment of Acute Catarrh of the Respiratory Passages.

Distressing as is the stage of acute discharge in cases of colds, the discomfort is slight compared with that of the subacute stage, when the discharge is thick and grumous and blocks up all the nasal passages. This part of an attack can, I have found, be cut down to a duration of only two or three days by the injection of a suitable vaccine. As soon as the patient is seen, smears and cultures should be made of the mucous discharge and the infecting organism ascertained. Whichever it may prove to be, the best procedure undoubtedly is to make a vaccine from the organism thus isolated. In the case of the *Bacillus septus* a stock vaccine may, however, be employed, in case of objection being taken to the expense, inasmuch as it appears to be a morphological entity. This perhaps holds, but to a less degree, in the case of the *Micrococcus catarrhalis*; but so great are the variations exhibited by different members of the bacillus of Friedlander group that but slight success may be anticipated from any vaccine other than that prepared from the patient's own organism. If possible, the patient should remain in bed for at least twenty-four hours subsequent to injection; but should this not be possible, then as soon as he has arrived at home for the evening is a suitable opportunity for injection.

The negative phase with an appropriate dose being usually over within twelve or eighteen hours, risk of relapse is only slight by eight or nine o'clock the next morning. The dose I usually employ is 150,000,000 or 200,000,000 of any of the above organisms.

I have now treated a considerable number of cases in this way, and always with very marked success. Some people appear to be immune to all 'cold' organisms, others are especially susceptible to one of the group, yet others to more than one. Injection during the subacute stage of an attack in those who fall under the second of these categories has, in each instance, not only markedly cut short the attack, but entirely prevented the onset of others, even for a period of over a year. In those who are susceptible to more than one of these organisms any given attack may be due to one only of their particular enemies or to more than one. Each organism produces its own type of cold, and from the unusual features presented mixed infection can be diagnosed even before smears or cultures have been examined. Should one organism only be found in the particular attack, then a vaccine of that organism alone may be given, or to it may be added a stock vaccine of the other organism to which the patient is also susceptible. In this way the attack may be shortened, and immunity also secured against future ones. Should mixed infection be found present, then, of course, a mixed vaccine should be administered.

The following are a few examples of cases treated according to this method.

Case 1 had for years been very susceptible to catarrhal attacks, which began in the naso-pharynx, producing a distinctly sore throat. A train journey, even for a few miles, would infallibly induce such an attack.

Advantage was taken of an acute attaek to isolate the *Bacillus septus*, whieh had beeu diagnosed beforehand as the causal agent. Upon the third day of the attack an injection of 250,000,000 organisms was given. Two days later the patient was well. Soon after he was called upon to undertake a long and tedious train journcy in the depth of winter. For the first time for years, no eold rcsulted, and during the subsequent ninc months, despite frequent train journeys, he remained entirely immune. On one or two oeeasions an impending attaek was felt, but immediately aborted.

Case 2 had at least half a dozen aeute colds every winter, always of the same type, obviously due to the *Bacillus septus*. At the beginning of last winter an unusually severe but typieal attaek eame on, and the *Bacillus septus* was isolated. Upon the seeond day of the attaek his index was 0·94. Upon the fifth day he felt very bad indeed, and aceordingly 275,000,000 organisms were injected. Improvement began within twenty-four hours, and was complete within forty-eight.

3 days after injection the index was 1·7
13 ,, ,, ,, ,, 1·1

Although the index would thus appear to have returned to normal within a fortnight, the immunity conferred lasted throughout the whole winter, despite repeated exposure to contagion.

Case 3 had had four attaeks of extreme severity within nine months. Upon one occasion the bacillus of Friedlander and *Bacillus septus* were both isolated, upon the second and third only the bacillus of Friedlander. Hardly was the patient convalescent from the third attack, which was one of the most severe eolds I have ever seen, all the accessory sinuses and middle ear being involved, when

a fourth attack came on. Upon this occasion the bacillus of Friedlander and *Micrococcus catarrhalis* were present in about equal numbers. The prostration of the patient was so extreme that I decided not even to delay while a vaccine was prepared, but on the fourth day of the attack 250,000,000 each of stock vaccines of the bacillus of Friedlander and *Micrococcus catarrhalis* were administered.

For forty-eight hours the patient was very bad, but then began to improve, and mended rapidly. Four months later she informed me that on several occasions she had felt one of her old attacks coming on, but in each instance it had been aborted completely within two or three hours.

Case 4 had been a martyr to repeated attacks of 'Friedlander' colds for years. The organism was isolated during an acute attack two years ago and two injections given, with the result that only one slight attack has occurred in all the subsequent interval, and this yielded to a single injection.

Numerous other cases have been similarly treated, and all have the same tale to tell—subsequent immunity from attacks. How long such immunity lasts it is impossible to say, but it is hardly advisable to allow more than three months to pass before giving a fresh injection. A vaccine once made will keep indefinitely, so that this trouble and expense need only once be incurred in the majority of cases.

The Opsonic Treatment of Tracheal Catarrh.

Tracheal catarrh, as we have seen, is usually initiated by the *Micrococcus catarrhalis;* unfortunately, however, secondary infection by other organisms often adds a

complicating factor. The treatment is rather difficult and results not very encouraging ; the best that can be hoped for is diminished secretion and comparative freedom from acute attacks of trachcitis.

Treatment may be carried out either by means of a vaccine prepared only from the *Micrococcus catarrhalis* isolated from a suitable specimen of tracheal mucus, or by a combined vaccine of the various organisms present. In the former case injection is begun with 150,000,000 to 250,000,000 organisms, and is, of course, controlled by determinations of the index to the *Micrococcus catarrhalis.* In the latter case a minimal dose of 250,000,000 of the mixed organisms is used at first. Inasmuch as the estimation of the indices to the various organisms would be far too tedious, that to one alone may be selected—best to the *Micrococcus catarrhalis.* A tri-weekly interval between injections will, however, prove sufficiently accurate. By means of such a combined vaccine I have secured a certain measure of success in two cases of chronic tracheitis, diminishing the discharge to a certain extent, and preventing the occurrence of any acute exacerbations. In a third case cure was complete. That extremely troublesome complaint of children whooping-cough would appear to offer exceptional opportunities for opsonic treatment. So far as I am aware no experiments have, however, been made in this direction.

The Treatment of Chronic Nasal Catarrh.

This, as has been mentioned, is apparently always due to the bacillus of Friedlander. In cases where the accessory air sinuses are not involved complete cure, both of the chronic attack and of the acute exacerbations,

is to be expected from opsonic treatment and daily douching with weak antiseptic washes, such as Glycothymoline. By these means I have completely cured cases of even ten years' standing. The index in such cases is usually above normal and between 1·2 and 1·4. A dose of 250,000,000 of the patient's own organism will usually raise this to 2·5 or over, and produce marked improvement within a week. Two or three such injections should prove sufficient.

When, however, extension has taken place to the frontal, ethmoidal, or antral sinus, the case is very much more difficult. In two such cases of about twenty years' standing I have sterilized the nose by adequately raising the index, only, however, to find it reinfected in a month or two from the accessory sinuses. Could free drainage from these be secured, complete cure might be expected ; as it is, the poor blood-supply and lymph-flow to the parts do not bring sufficient opsonin to ensure the death of the infecting organisms. Perhaps very prolonged treatment might secure this much-desired result. One very important result is, however, certainly secured, and that is the prevention of acute outbursts of the nasal catarrh.

CHAPTER IX

OPSONIC TREATMENT IN CASES DUE TO INFECTION BY THE *BACILLUS COLI COMMUNIS*, *MICROCOCCUS MELITENSIS*, *BACILLUS PARALYTICANS* (OF FORD ROBERTSON), *MICROCOCCUS NEOFORMANS*, AND MENINGOCOCCUS

The *Bacillus coli communis* is especially associated with disease of the abdominal organs, setting up such conditions as peritonitis, cystitis, urethritis, abscesses in and around the kidneys, enteritis, perityphlitis, and inflammation of the gall bladder and its ducts. It also occasionally is the cause of Empyema and Puerperal Fever.

Wright[1] has recorded the successful treatment of the following cases :

1. One of cholecystitis, which has continued for sixteen years.

2. One of acute coli infection of the biliary passages, where, after removal by operation of an impacted calculus, the fever and jaundice continued, and the bile was flowing away through the external wound, probably from plugging of the bile-duct by inspissated mucus.

3. One which had been operated upon two months previously, fourteen stones being removed from the gall-bladder. The sinus remained open, and the patient made little improvement. An injection of 200,000,000 organisms was given, and the index raised to 1·8 ; closure of

[1] Pathological Society, January 16, 1906.

the sinus was followed by a rise of temperature and reopening of the sinus. A second injection produced reclosure of the sinus. A rigor then occurred, and the sinus again opened. Owing to self-inoculation, the index rose to 4, subsequently to fall with final closure of the sinus.

Most cases of appendicitis and appendical abscess are due to the *Bacillus coli communis*. Most valuable information, both in diagnosis, prognosis, and treatment, would probably be afforded by a study of the opsonic index in these cases ; so far as I am aware, no investigations upon this important point have been recorded.

Cases of bacilluria are frequently due to the *Bacillus coli communis*, especially when cystitis complicates a tubercular bladder. In these instances little progress is often made under injections of T.R. alone. Upon attention being simultaneously directed to the secondary infection, marked improvement is at once noticeable. The same holds true in the treatment of tuberculous kidneys. The initial dose in coli infection is 100,000,000 to 200,000,000, whilst a maximum dose of 1,000,000,000 may ultimately be attained.

The Micrococcus Melitensis.

The fact that Malta fever is a systemic infection would seem to render opsonic injections inadvisable. Wright, however, advocates their use in comparatively light attacks, when the fever is likely to run on for months without any severe intoxication of the system, and where the imperfect development of the agglutination reaction seems to indicate that the immunizing impulses are in default.

He has successfully treated a case of localized infection supervening upon an attack of Malta fever.

Bassett Smith,[1] following up the apparently successful treatment by Reid of nine cases of Malta fever by means of a vaccine, observed the results of such treatment in sixty-one cases, to which 224 injections were given. These cases comprised all grades in the disease, from the severe undulant type to the intermittent. The initial dose employed was usually about 50,000,000 organisms, and this was but rarely exceeded, the interval between the injections being ten days. The negative phase was frequently very short or altogether absent, a steady rise being commonly observed.

No relationship was found to exist between the curves of the opsonic indices and the agglutination reactions of the patient's sera. Bassett Smith concluded that the vaccine treatment of Malta fever appears in a certain number of cases to produce a beneficial result, the severity of the symptoms being diminished, the general condition improved, and the duration of the disease curtailed; but that in the more severe type of case, with higher fever and evidence of severe intoxication, the method appears to have a deleterious instead of a favourable action.

I would suggest that the more frequent administration of much smaller doses, as in streptococcal and gonococcal septicæmias, might possibly secure more favourable results.

The Bacillus Paralyticans.

Numerous attempts have been made to isolate from the blood and cerebro-spinal fluid of cases of General

[1] *Journal of Hygiene*, January, 1907, p. 115.

Paralysis of the Insane and of Tabes Dorsalis an organism or organisms which might prove to stand in a causal relationship to this disease or to the congestive seizures.

Ford Robertson and McRae claimed to have demonstrated the constant presence of an organism of the diphtheroid group, to which they gave the name *Bacillus paralyticans*, in the blood, cerebro-spinal fluid, and brain tissues. Other observers, among whom may be mentioned Eyre and Flashman, have, however, shown that there is hardly any part of the body where diphtheroid organisms had been obtained by Robertson in cases of General Paralysis from which similar organisms could not be obtained in cases free from any semblance of insanity. The difficulties in technique are so great, and the risks of contamination in taking cultivations so considerable, that variable results are almost inevitable in the hands of different observers. It may be mentioned that the psychological moment for taking cultures is as soon as possible after a congestive attack, for leucocytosis is rapidly developed, and in an hour or two the phagocytic action of the leucocytes may destroy all the organisms in the blood-stream. Sufficient attention to this point does not appear to have been paid by all observers. Ford Robertson now considers that a second organism, to which he has given the name *Bacillus paralyticans brevis*, is also concerned in the production of a certain proportion of cases of General Paralysis. Candler[1] altogether failed on forty-one occasions in twenty-four cases to find either of these organisms, while G. M. Robertson[2] upon fifteen occasions in seven cases of undoubted General Paralysis recovered a diphtheroid organism from the blood or cerebro-spinal fluid, which, however, appeared to differ

[1] *Lancet*, August 17, 1907, p. 450. [2] *Ibid.*, p. 449.

from either of Ford Robertson's forms. Sufficient evidence has not yet been accumulated to warrant the view that any definite member of the diphtheroid group is responsible for the production of General Paralysis, although it seems likely that the presence of these organisms is more than a coincidence, and important discoveries may soon be anticipated.

O'Brien[1] details the result of opsonic determinations with Ford Robertson's original *Bacillus paralyticans* upon seven cases of this disease. The indices showed great fluctuations, leading him to the conclusion that the infection is a systemic one. Injections of a vaccine were given about every fourteen days, and marked improvement in the symptoms claimed to be noticed.

These results must be received with great caution, in view of Ford Robertson's modified opinion of the causal relationship of this organism to the disease, and in consideration of the fact that remissions in the course of General Paralysis are very common. In so dread a disease no chance of doing good should, however, be neglected and in the event of the isolation of a diphtheroid organism from cultures of the cerebro-spinal fluid taken during or immediately after a congestive attack, the administration of a vaccine prepared from this organism would appear to be a justifiable—nay, advisable—proceeding.

The Micrococcus Neoformans.

The contention of Doyen that this organism is the true cause of carcinomatous tumours has not been accepted by pathologists in this country; for not only is it found in the vicinity of carcinomata, but also in that of sarco-

[1] *Journal American Medical Association*, 1906, p. 2180.

mata and such benign growths as adenomata. Inoculation experiments upon rats and mice have also completely failed to produce a malignant tumour.

Successful treatment by means of a vaccine was recorded by Wright in a case of cancer of the larynx. Death, however, ensued in about six months, and was found post-mortem to be due to cancer.

Jacobs and Geets[1] recorded the results of treatment in thirty-seven cases of mammary carcinoma. They regard the *Micrococcus neoformans* as the cause of the cancerous cachexia. The index in these cases was found usually to be below 0·8. Cases in which the index failed to rise after two injections they considered hopeless from exhaustion of the defensive powers.

The results of treatment seem to be decrease of surrounding infiltration, reduction in the size of the nodules, which usually become freely movable, great improvement in the patient's appearance and general condition, and diminution of pain. This they hold to be the time for operation. They tabulate their results as follows :

'Cure' maintained after several months in	7	cases.
Lasting improvement in	12	,,
Transient result in	7	,,
No result in	11	,,
Total	37	,,

The opinion at the London Cancer Hospital is that as a curative agent a vaccine of the *Micrococcus neoformans* is valueless, and its employment has therefore been entirely abandoned at that institution. It may, however, well be left to any inoperable case of cancer to decide whether employment of this harmless agent shall be made in the remote hope of the case being brought within the zone of

[1] *Lancet*, April 7, 1906, p. 964.

operability. Admitting that the *Micrococcus neoformans* is not the cause of cancer, it cannot, however, be denied that it is almost always associated with the cancerous tumour.

The Meningococcus.

The complete failure of various varieties of anti-meningococcic sera to influence favourably the course of the disease during the recent epidemics at Belfast and Glasgow, and the occasional success of a streptococcal vaccine in cases of streptococcal septicæmia, have encouraged efforts in a similar direction in cases of cerebro-spinal meningitis. Houston and Rankin[1] found the index was always high after the fifth day, and that this was a useful aid to diagnosis in difficult cases. The index of the blood-serum was higher than that of the cerebro-spinal fluid. Rundle and Mottram[2] have recorded a successful result in a case in which the prognosis was distinctly bad. The index was 0·7 when an injection of 200,000 organisms was given; next day it had risen to 1·5. In the subsequent twenty days four doses of 500,000 organisms were given, each followed by negative and positive phases. Recorded cases of successful treatment are so far very few, but I have heard privately of two other such instances.

[1] *Lancet*, September 7, 1907, p. 704.
[2] *Ibid.*, July 27, 1907, p. 220.

CHAPTER X

OPSONIC TREATMENT IN EYE DISEASES

Brief reference has already been made to the treatment of Tubercular Keratitis and Iritis, of Ulcus Serpens Corneæ, and of Gonococcal Conjunctivitis, by injections of bacterial vaccines.

Ophthalmic surgeons would probably be the first to admit that little further progress in ophthalmology is to be expected from surgery pure and simple. The prime essential is increase of knowledge in the pathology of such conditions as Trachoma, Mooren's Ulcer, Spring Catarrh, and Sympathetic Ophthalmia. Should a bacterial origin be established for these, treatment upon opsonic lines will hold out considerable promise of success.

An important advance in the diagnosis of doubtful tubercular infections has been afforded by the discovery of what is known as Calmette's ophthalmo-reaction.

Von Pirket[1] showed that if a small quantity of tuberculin be introduced into a scarification on the arm of a tuberculous subject a reaction occurs, which is but rarely obtained with healthy individuals. After forty-eight hours some redness and œdema result, and a papule resembling that of vaccinia appears ; within a week this dries up and the reaction subsides.

[1] *Deut. Med. Woch.*, 1907, May 23 and 30.

Calmette[1] observed that absorption took place so readily through the conjunctival mucous membrane that the application to its surface of tuberculin had an analogous result to the introduction through the scarification wound. To avoid the irritating effect upon the conjunctiva of the glycerine in ordinary tuberculin, he precipitated the tuberculin with 95 per cent. of alcohol, dried the resultant powder, and prepared a 1 per cent. solution in sterile distilled water. One or two drops of this are instilled into one eye. The first signs of a positive reaction appear in three to five hours—congestion of the palpebral conjunctiva is soon succeeded by an œdematous condition ; the carunele swells, becomes reddened and covered with fibrinous exudate. In some cases this is all that occurs ; in others the vascular engorgement increases and is accompanied by lachrymation. The maximum effect is produced in between six and ten hours, when all the appearances of an acute muco-purulent conjunctivitis may be present. There is, however, but little discomfort, and no pain or elevation of temperature, the cornea is not involved, nor is there injection of the episcleral vessels or deeper structures. In children the phenomena subside in about eighteen hours ; in adults in two or three days, or even longer.

The only contra-indication to the employment of the test is conjunctivitis in the eye to be tested ; no effect is produced in the other eye. In non-tubercular subjects no reaction at all is produced, or but slight transitory redness of the conjunctiva, unattended by exudation or lachrymation.

This test would appear to be a practically reliable means of diagnosing tuberculosis wherever situated.

[1] *Presse Med.*, June 19, 1907.

Thus Calmette obtained a positive reaction in twelve cases of pulmonary phthisis, in two of tuberculous pleurisy, and in two of tuberculous glands ; while negative results were obtained in cases of hysteria, tabes, heart disease, katatonia, influenza, cerebral sclerosis, lymphangitis, and acute rheumatism. Numerous other observers have confirmed Calmette's results, and the test would appear to have a peculiar value in deciding whether a supposedly cured case of pulmonary phthisis is really free from infection.

It is with cases of tuberculosis of the eye that we are, however, here concerned, and considerable light has been thrown upon the nature of the infection in various cases of phlyctenule, keratitis, conjunctivitis, episcleritis, choroiditis, and optic neuritis, and the difficulty of deciding whether any given case is really tubercular in nature would appear no longer to exist.

Thus Brunetière[1] has recorded its value in discriminating between interstitial keratitis due to syphilis and to the tubercle bacillus. Anbault and Lafon[2] obtained positive reactions in a case of solitary tubercle of the choroid, in two of phlyctenulæ, in episcleritis, in tubercular interstitial keratitis, and in optic neuritis with a choroidal nodule, also in four cases of healed phlyctenule. Stephenson[3] has employed it in over thirty cases, among which were six cases in children of *relapsing ulceration of the cornea.* A positive result was obtained in each case, though only two of them showed tubercular lesions elsewhere. In one case of recent phlyctenular keratitis the result was negative. In three cases of

[1] *Gaz. Hebd. de la Soc. Méd. de Bordeaux*, July 18, 1907.
[2] *Ibid.*, August 14, 1907.
[3] *British Medical Journal*, October 19, 1907, p. 1038.

choroiditis in young women, free, apparently, from traces of syphilis, the reaction was positive, though no tuberculous focus could be found elsewhere. Of eight cases of *interstitial keratitis*, five showed obvious signs of inherited syphilis, and in these the result was negative ; in the three others it was positive.

Of three cases of *episcleritis*, one had enlarged cervical, axillary, and inguinal glands, and the result was positive ; in the two others it was negative.

One case of *tubercle of the iris*, one of *tubercle of the cornea*, and two of *chronic iridocyclitis* also gave positive results.

The extreme value of this method of diagnosis in doubtful tuberculous infections of the eye, dispensing, as it does, with the necessity for estimations of the opsonic index of the blood, is at once obvious ; but the fact that it is a test for tuberculous infection anywhere must not be lost sight of, especially in children, who are so prone to undiscoverable tuberculous bronchial and mesenteric glands.

The following table (Table XIII.) shows how very variable is the opsonic index in cases of tuberculosis of the eye, sometimes being much above unity, sometimes much below it ; and inasmuch as a case of undoubted tubercular origin may have an index within the normal limits, such an index throws no light upon the diagnosis in a doubtful case, whereas Calmette's reaction should prove conclusive.

The diagnosis once established, treatment by means of tuberculin is to be none the less controlled by determinations of the opsonic index. Doses of 0·0001 milligramme or 0·0002 milligramme suffice to begin with, and intervals of three to four weeks between injections

are often found advisable. As to whether these infections are always of the human or bovine type, or sometimes of the one, sometimes of the other, we know not at all. If treatment with tuberculin of the human type be persisted in, uniform success should be secured, but intervals of six months or more are often necessary. Choroidal nodules may be watched disappearing by means of the ophthalmoscope, gradual shrinking occurring till

TABLE XIII

Case.	Nature of Case.	Index.
1	Interstitial keratitis	2·2
2	Phlyctenules	1·9
3	Kerato-iritis with mutton-fat deposits ..	1·4
4	Choroidal nodule	1·25
5	Kerato-iritis with phlyctenules	1·1
6	Tubercular cyst of iris	0·87
7	Neuro-choroidal retinitis	0·8
8	Choroidal tubercle	0·7
9	Interstitial keratitis	0·7
10	Keratitis with glands in the neck	0·55
11	Keratitis with cervical and abdominal glands	0·5

nothing is seen but a white scar or total absorption takes place. It may well be that more expeditious cure might be secured in some cases by the employment of tuberculin prepared from the bovine type ; a case not doing well with the human variety may be taken to indicate the advisability of continuing treatment with the bovine tuberculin.

In addition to the affections already mentioned, scope for opsonic treatment is afforded in conjuncti-

vitis due to Friedlander's bacillus or to the *Bacillus lacunatus* of Morax-Axenfeld, in various other forms of corneal ulceration, and in cases which have become infected at or subsequent to operation. Conjunctivitis due to Friedlander's bacillus yields to none of the ordinary remedies, and is especially suitable for this form of treatment. That caused by the *Bacillus lacunatus* shows great tendency to become chronic and resist treatment, whereas it responds very readily to injections of a vaccine. The organism, though easy to isolate, is very difficult to cultivate satisfactorily; the preparation of a vaccine is therefore no easy matter. Two or three injections of 100,000,000 organisms at bi- or tri-weekly intervals, followed by one of 250,000,000 usually suffice to cure a bad case. Determinations of the index may be dispensed with, the clinical appearances being sufficient guide as to the appropriate time for repeating the injections.

Corneal Ulcers.

The bacteriology of these is not well known. The tubercle bacillus and pneumococcus are certain causes of some chronic varieties. Acute ulceration may be due to streptococci, staphylococci, gonococci, *Bacillus coli communis*, *Bacillus pyocyaneus*, and other organisms. No matter how high the index may be to an infecting organism in these cases, immediate injection of a stock vaccine should be made as soon as the preparation has been identified; the preparation of a fresh vaccine from the patient's own bacteria should then be proceeded with, and a fresh injection made, should no response to the stock vaccine be noticeable. The success attending this pro-

cedure in a case of acute gonococcal conjunctivitis has already been described.

The following case, under the care of Professor McHardy, at the Royal Eye Hospital, is also interesting : The patient had already had one eye removed for chronic ulcerative keratitis, going on to perforation, shrinking of the globe, and considerable pain. About eighteen months subsequently the second eye was also attacked ; general superficial erosion of the cornea went on to infiltration of the more superficial, then of the deeper layers of the cornea ; the tension fell considerably, and vision was practically nil, only dim perception of light being possible. Cultures from the surface of the globe yielded large cocci not staining by Gram's method, which were certainly not the *Micrococcus catarrhalis*, and diplococci which morphologically resembled the pneumococcus, but could not be isolated. Upon the chance of the infection being a pneumococcal one, two injections of a vaccine were given without producing any good result ; on the contrary, the condition became rather worse. The vision was so bad that an iridectomy was decided on. The iris, when seized by the forceps, simply tore at once it was so pulpy ; cultures were made from this small portion of iris and from scrapings of an eroded portion of the cornea, and the same non-Gram-staining coccus obtained from both. The organism so far has not been identified, but a vaccine was made of it as a last hope. A first injection of 250,000,000 organisms, the index being 0·5, was followed ten days later, when the index was 0·8, by a second of like amount ; seventeen days after the first injection, the index being 1·5, the eye began definitely to improve, and steadily continued to do so. Twenty-eight days after the second injection the index was 2·6, and a further

injection of 400,000,000 given. The eye was now very much better ; vision was returning, fingers being seen at about 1 foot. In another twenty-six days the patient could discern faces fairly well, and a further injection of 500,000,000 cocci was given. A fortnight later vision was further improved, and the patient was discharged. When seen two months later, vision, both near and for distance $= \frac{1}{60}$; the cornea was diffusely nebulous ; the eye was quite quiet, and vision had decidedly improved since the patient had left the hospital.

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